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FILE 'USPATFULL' ENTERED AT 13:47:21 ON 13 NOV 2003
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FILE 'CAPLUS' ENTERED AT 13:47:21 ON 13 NOV 2003
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=> s salbutamol
L1         5021 SALBUTAMOL

=> s beclomethasone dipropionate
L2         1953 BECLOMETHASONE DIPROPIONATE

=> s l1 and l2
L3          407 L1 AND L2

=> s l3 and asthma
L4          241 L3 AND ASTHMA

=> s glaxo/as
'AS' IS NOT A VALID FIELD CODE
'AS' IS NOT A VALID FIELD CODE
L5            0 GLAXO/AS
```

09 920340

```
=> s glaxo/ass
'ASS' IS NOT A VALID FIELD CODE
'ASS' IS NOT A VALID FIELD CODE
L6            0 GLAXO/ASS

=> help
To see the field codes for search terms in an L-number, enter "DISPLAY
QUERY" followed by the L-number at an arrow prompt.  To see the field
codes for search terms in a saved query, enter "ACTIVATE" and the
query name, followed by '/Q' at an arrow prompt.

=> s glaxo
L7         1991 GLAXO

=> s l7 and l4
L8           28 L7 AND L4

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9            28 DUP REM L8 (0 DUPLICATES REMOVED)

=> d l9 1-28 ab bib

L9   ANSWER 1 OF 28  USPATFULL on STN
AB      The invention relates to a method of producing an agglomerate of drug
        and solid binder. The process involves producing individual agglomerate
        particles and then converting the convertible amorphous content of same,
        following agglomeration, by the application of, for example, moisture.
        Agglomerates capable of conversion as well as the finished agglomerates
        and oral and nasal dosing systems including same are also contemplated.
        The process produces agglomerates which are rugged but which will
        produce an acceptable fine particle fraction during dosing.
AN      2003:225373  USPATFULL
TI      Preparation of powder agglomerates
IN      Yang, Tsong-Toh, Warren, NJ, UNITED STATES
PI      US 2003157184      A1   20030821
AI      US 2002-326327     A1   20021219 (10)
RLI     Continuation of Ser. No. US 2001-824377, filed on 2 Apr 2001, GRANTED,
        Pat. No. US 6503537 Continuation of Ser. No. US 1998-42973, filed on 17
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Mar 1998, ABANDONED
PRAI US 1997-41055P 19970320 (60)
DT Utility
FS APPLICATION
LREP SCHERING-PLOUGH CORPORATION, PATENT DEPARTMENT (K-6-1, 1990), 2000 GALLOPING HILL ROAD, KENILWORTH, NJ, 07033-0530
CLMN Number of Claims: 63
ECL Exemplary Claim: 1
DRWN 4 Drawing Page(s)
LN.CNT 1410
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 2 OF 28 USPATFULL on STN
AB The present invention relates to novel pharmaceutical aerosol formulations comprising: (A) a therapeutic agent in the form of particles coated by at least one coating excipient and at least one surfactant, in suspension in (B) a liquefied propellant gas for the administration of therapeutic agents particularly by the pulmonary route and to process for preparing these formulations. It also relates to novel particles suitable for use in such formulations.
AN 2003:225221 USPATFULL
TI Pharmaceutical aerosol formulation
IN Cavaillon, Pascal, Evreux Cedex, FRANCE
Llorca, Nathalie, Evreux Cedex, FRANCE
Louis, Olivier, Evreux Cedex, FRANCE
Rosier, Patrick, Evreux Cedex, FRANCE
PI US 2003157032 A1 20030821
AI US 2003-364257 A1 20030211 (10)
RLI Continuation of Ser. No. US 2000-673426, filed on 12 Dec 2000, PENDING A 371 of International Ser. No. WO 1999-EP2535, filed on 15 Apr 1999, UNKNOWN
PRAI GB 1998-8152 19980418
GB 1998-14709 19980708
DT Utility
FS APPLICATION
LREP DAVID J LEVY, CORPORATE INTELLECTUAL PROPERTY, GLAXOSMITHKLINE, FIVE MOORE DR., PO BOX 13398, RESEARCH TRIANGLE PARK, NC, 27709-3398
CLMN Number of Claims: 43
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 956
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 3 OF 28 USPATFULL on STN
AB The present invention is concerned with pharmaceutical formulations comprising a combination of tiotropium and mometasone and the use of such formulations in medicine, particularly in the prophylaxis and treatment of respiratory diseases.
AN 2003:201397 USPATFULL
TI Medical combinations comprising tiotropium and mometasone
IN Gavin, Brian Charles, Rathfarnfam, IRELAND
Garrett, Ronique Nichele, Durham, NC, UNITED STATES
Roche, Trevor Charles, Ware, UNITED KINGDOM
PI US 2003139383 A1 20030724
AI US 2002-257704 A1 20021015 (10)
WO 2001-GB1646 20010411
PRAI GB 2000-9605 20000418
DT Utility
FS APPLICATION
LREP DAVID J LEVY, CORPORATE INTELLECTUAL PROPERTY, GLAXOSMITHKLINE, FIVE MOORE DR., PO BOX 13398, RESEARCH TRIANGLE PARK, NC, 27709-3398
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN No Drawings

LN.CNT 378
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 4 OF 28 USPATFULL on STN
AB The present invention is concerned with pharmaceutical formulations comprising a combination of salmeterol and budesonide and the use of such formulations in medicine, particularly in the prophylaxis and treatment of respiratory diseases.
AN 2003:181480 USPATFULL
TI Medical combination comprising salmeterol and budesonide
IN Gavin, Brian Charles, Rathfarnfam, IRELAND
PI US 2003125313 A1 20030703
AI US 2002-257642 A1 20021015 (10)
WO 2001-GB1643 20010411
PRAI GB 2000-9613 20000418
DT Utility
FS APPLICATION
LREP DAVID J LEVY, CORPORATE INTELLECTUAL PROPERTY, GLAXOSMITHKLINE, FIVE MOORE DR., PO BOX 13398, RESEARCH TRIANGLE PARK, NC, 27709-3398
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 334
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 5 OF 28 USPATFULL on STN
AB The present invention is concerned with pharmaceutical formulations comprising a combination of tiotropium and rofleponide and the use of such formulations in medicine, particularly in the prophylaxis and treatment of respiratory diseases.
AN 2003:174011 USPATFULL
TI Medical combinations comprising tiotropium and rofleponide
IN Gavin, Brian Charles, Rathfarnfam, IRELAND
PI US 2003119859 A1 20030626
AI US 2002-257703 A1 20021015 (10)
WO 2001-GB1627 20010411
PRAI GB 2000-9592 20000418
DT Utility
FS APPLICATION
LREP DAVID J LEVY, CORPORATE INTELLECTUAL PROPERTY, GLAXOSMITHKLINE, FIVE MOORE DR., PO BOX 13398, RESEARCH TRIANGLE PARK, NC, 27709-3398
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 354
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 6 OF 28 USPATFULL on STN
AB The present invention is concerned with pharmaceutical formulations comprising a combination of tiotropium and budesonide and the use of such formulations in medicine, particularly in the prophylaxis and treatment of respiratory diseases.
AN 2003:173954 USPATFULL
TI Medical combinations comprising tiotropium and budesonide
IN Gavin, Brian Charles, Rathfarnfam, IRELAND
PI US 2003119802 A1 20030626
AI US 2002-257641 A1 20021015 (10)
WO 2001-GB1641 20010411
PRAI GB 2000-9583 20000418
DT Utility
FS APPLICATION
LREP DAVID J LEVY, CORPORATE INTELLECTUAL PROPERTY, GLAXOSMITHKLINE, FIVE MOORE DR., PO BOX 13398, RESEARCH TRIANGLE PARK, NC, 27709-3398
CLMN Number of Claims: 7

ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 332
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 7 OF 28 USPATFULL on STN
AB Elongated drug, especially **salbutamol** sulphate, and/or carrier particles, especially lactose, pharmaceutical compositions comprising the same, and use of the elongated particles in the manufacture of a medicament for the treatment of respiratory disease.
AN 2003:172670 USPATFULL
TI Compositions for inhalation
IN Larhrib, El Hassane, London, UNITED KINGDOM
Marriott, Christopher, London, UNITED KINGDOM
Martin, Gary Peter, London, UNITED KINGDOM
Pritchard, John Nigel, Middlesex, UNITED KINGDOM
Zeng, Xian Ming, Essex, UNITED KINGDOM
PA Glaxo Wellcome Inc., Research Triangle Park, NC (non-U.S. corporation)
PI US 2003118514 A1 20030626
AI US 2002-227433 A1 20020826 (10)
RLI Continuation of Ser. No. US 2000-646112, filed on 13 Nov 2000, PENDING A 371 of International Ser. No. WO 1999-EP1967, filed on 24 Mar 1999, UNKNOWN
PRAI GB 1998-6462 19980326
DT Utility
FS APPLICATION
LREP BACON & THOMAS, PLLC, 625 SLATERS LANE, FOURTH FLOOR, ALEXANDRIA, VA, 22314
CLMN Number of Claims: 27
ECL Exemplary Claim: 1
DRWN 3 Drawing Page(s)
LN.CNT 1110
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 8 OF 28 USPATFULL on STN
AB The present invention is concerned with pharmaceutical formulations comprising a combination of salmeterol and mometasone and the use of such formulations in medicine, particularly in the prophylaxis and treatment of respiratory diseases.
AN 2003:166679 USPATFULL
TI Medical combinations comprising mometasone and salmeterol
IN Gavin, Brian Charles, Rathfarnfam, IRELAND
Garrett, Ronique Nichele, Durham, NC, UNITED STATES
Roche, Trevor Charles, Ware, UNITED KINGDOM
PI US 2003114537 A1 20030619
AI US 2002-257640 A1 20021015 (10)
WO 2001-GB1637 20010411
PRAI GB 2000-9609 20000418
DT Utility
FS APPLICATION
LREP DAVID J LEVY, CORPORATE INTELLECTUAL PROPERTY, GLAXOSMITHKLINE, FIVE MOORE DR., PO BOX 13398, RESEARCH TRIANGLE PARK, NC, 27709-3398
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN 2 Drawing Page(s)
LN.CNT 445
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 9 OF 28 USPATFULL on STN
AB The present invention is concerned with pharmaceutical formulations comprising a combination of tiotropium and fluticasone propionate and the use of such formulations in medicine, particularly in the prophylaxis and treatment of respiratory diseases.
AN 2003:165415 USPATFULL

TI Medical combinations comprising tiotropium and fluticasone proprionate
IN Gavin, Brian Charles, Rathfarnfam, IRELAND
PI US 2003113269 A1 20030619
AI US 2002-257643 A1 20021015 (10)
WO 2001-GB1631 20010411
PRAI GB 2000-9606 20000418
DT Utility
FS APPLICATION
LREP DAVID J LEVY, CORPORATE INTELLECTUAL PROPERTY, GLAXOSMITHKLINE, FIVE MOORE DR., PO BOX 13398, RESEARCH TRIANGLE PARK, NC, 27709-3398
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 329
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 10 OF 28 USPATFULL on STN
AB The present invention is concerned with pharmaceutical formulations comprising a combination of (R,R)-formoterol and budesonide and the use of such formulations in medicine, particularly in the prophylaxis and treatment of respiratory diseases.
AN 2003:159895 USPATFULL
TI Medical combinations comprising formoterol and budesonide
IN Gavin, Brian Charles, Rathfarnfam, IRELAND
PI US 2003109510 A1 20030612
AI US 2002-257711 A1 20021015 (10)
WO 2001-GB1628 20010411
PRAI GB 2000-95844 20000418
DT Utility
FS APPLICATION
LREP DAVID J LEVY, CORPORATE INTELLECTUAL PROPERTY, GLAXOSMITHKLINE, FIVE MOORE DR., PO BOX 13398, RESEARCH TRIANGLE PARK, NC, 27709-3398
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 344
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 11 OF 28 USPATFULL on STN
AB The present invention is concerned with pharmaceutical formulations comprising a combination of salmeterol and rofleponide and the use of such formulations in medicine, particularly in the prophylaxis and treatment of respiratory diseases.
AN 2003:141032 USPATFULL
TI Respiratory compositions
IN Gavin, Brian Charles, Rathfarnfam, IRELAND
PI US 2003096874 A1 20030522
AI US 2002-257701 A1 20021015 (10)
WO 2001-GB1630 20010411
PRAI GB 2000-9617 20000418
DT Utility
FS APPLICATION
LREP DAVID J LEVY, CORPORATE INTELLECTUAL PROPERTY, GLAXOSMITHKLINE, FIVE MOORE DR., PO BOX 13398, RESEARCH TRIANGLE PARK, NC, 27709-3398
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 332
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 12 OF 28 USPATFULL on STN
AB The invention involves administration of an immunostimulatory nucleic acid alone or in combination with an **asthma**/allergy medicament for the treatment or prevention of **asthma** and allergy in

subjects. The combination of drugs are administered in synergistic amounts or in various dosages or at various time schedules. The invention also relates to kits and compositions concerning the combination of drugs.

AN 2003:127633 USPATFULL
TI Immunostimulatory nucleic acids for the treatment of **asthma** and allergy
IN Bratzler, Robert L., Concord, MA, UNITED STATES
Petersen, Deanna M., Newton, MA, UNITED STATES
Fouron, Yves, Marlboro, MA, UNITED STATES
PI US 2003087848 A1 20030508
AI US 2001-776479 A1 20010202 (9)
PRAI US 2000-179991P 20000203 (60)
DT Utility
FS APPLICATION
LREP Helen C. Lockhart, c/o Wolf Greenfield & Sacks, P.C., Federal Reserve Plaza, 600 Atlantic Avenue, Boston, MA, 02210
CLMN Number of Claims: 36
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 8826
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 13 OF 28 USPATFULL on STN
AB The invention relates to a method of producing an agglomerate of drug and solid binder. The process involves producing individual agglomerate particles and then converting the convertible amorphous content of same, following agglomeration, by the application of, for example, moisture. Agglomerates capable of conversion as well as the finished agglomerates and oral and nasal dosing systems including same are also contemplated. The process produces agglomerates which are rugged but which will produce an acceptable fine particle fraction during dosing.

AN 2003:125280 USPATFULL
TI Preparation of powder agglomerates
IN Yang, Tsong-Toh, Warren, NJ, UNITED STATES
PI US 2003085480 A1 20030508
AI US 2002-238423 A1 20020910 (10)
RLI Continuation of Ser. No. US 2001-901205, filed on 9 Jul 2001, PENDING
Continuation of Ser. No. US 2001-824377, filed on 2 Apr 2001, PENDING
Continuation of Ser. No. US 1998-42973, filed on 17 Mar 1998, ABANDONED
PRAI US 1997-41055P 19970320 (60)
DT Utility
FS APPLICATION
LREP SCHERING-PLOUGH CORPORATION, PATENT DEPARTMENT (K-6-1, 1990), 2000 GALLOPING HILL ROAD, KENILWORTH, NJ, 07033-0530
CLMN Number of Claims: 63
ECL Exemplary Claim: 1
DRWN 4 Drawing Page(s)
LN.CNT 1414
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 14 OF 28 USPATFULL on STN
AB A combination of therapeutic agents useful in the treatment of obstructive airways and other inflammatory diseases comprising (i) an adenosine A.sub.2A receptor agonist; and (ii) an anti-cholinergic agent, preferably comprising a member selected from the group consisting of tiotropium and derivatives thereof; the combination being therapeutically effective in the treatment of the diseases when administered by inhalation; as well as to a method of treating the obstructive airways and other inflammatory diseases comprising administering separately, simultaneously or sequentially to the mammal by inhalation a therapeutically effective amount of the combination of therapeutic agents; as well as to a pharmaceutical composition comprising a pharmaceutically acceptable carrier together with the

combination of therapeutic agents; as well as to a product containing the compounds of the combination for separate, simultaneous or sequential administration by inhalation to a mammal for the treatment of obstructive airways and other inflammatory diseases. It is preferred that the anti-cholinergic agent component be tiotropium bromide.

AN 2003:17922 USPATFULL

TI Combination of an adenosine A2A-receptor agonist and tiotropium or a derivative thereof for treating obstructive airways and other inflammatory diseases

IN Yeadon, Michael, Sandwich, UNITED KINGDOM
Watson, John W., Ledyard, CT, UNITED STATES
Armstrong, Roison Anne, Mystic, CT, UNITED STATES

PA Boehringer Ingelheim Pharma KG, Ingelheim, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)

PI US 2003013675 A1 20030116

AI US 2002-154561 A1 20020524 (10)

PRAI US 2001-293530P 20010525 (60)
US 2001-303934P 20010709 (60)

DT Utility

FS APPLICATION

LREP BOEHRINGER INGELHEIM CORPORATION, 900 RIDGEBURY ROAD, P. O. BOX 368, RIDGEFIELD, CT, 06877

CLMN Number of Claims: 42

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 4413

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 15 OF 28 USPATFULL on STN

AB A method of treating in a human or animal a condition capable of treatment by oral or nasal inhalation has been found. The method comprises administering a medicinal aerosol formulation comprising a selected medicament under conditions where the amount of the selected drug delivered to the site of action, e.g. the lungs, is maximized.

AN 2003:196936 USPATFULL

TI Method of administering a medicinal aerosol formulation

IN Adjei, Akwete L., Bridgewater, NJ, United States
Stefanos, Simon, Morris Plains, NJ, United States
Zhu, Yaping, Highland Park, NJ, United States

PA Aeropharm Technology Incorporated, Edison, NJ, United States (U.S. corporation)

PI US 6596261 B1 20030722

AI US 2000-702194 20001030 (9)

PRAI US 2000-177982P 20000125 (60)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Hartley, Michael G.; Assistant Examiner: Haghightian, M.

LREP Frommer Lawrence & HaugLLP

CLMN Number of Claims: 9

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 751

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 16 OF 28 USPATFULL on STN

AB A series of 2-(Purin-9-yl)-tetrahydrofuran-3,4-diol derivatives with broad anti-inflammatory properties which inhibit leukocyte recruitment and activation and which are agonists of the adenosine 2a receptor are described.

AN 2003:74395 USPATFULL

TI 2-(purin-9-yl)-Tetrahydrofuran-3,4-diol derivatives

IN Allen, David George, Stevenage, UNITED KINGDOM
Chan, Chuen, Stevenage, UNITED KINGDOM

Cook, Caroline Mary, Stevenage, UNITED KINGDOM
Cousins, Richard Peter Charles, Stevenage, UNITED KINGDOM
Cox, Brian, Stevenage, UNITED KINGDOM
Dyke, Hazel Joan, Cambridge, UNITED KINGDOM
Ellis, Frank, Stevenage, UNITED KINGDOM
Geden, Joanna Victoria, Aston Science Park, UNITED KINGDOM
Hobbs, Heather, Stevenage, UNITED KINGDOM
Keeling, Suzanne Elaine, Stevenage, UNITED KINGDOM
Redgrave, Alison Judith, Stevenage, UNITED KINGDOM
Swanson, Stephen, Stevenage, UNITED KINGDOM
Whitworth, Caroline, Stevenage, UNITED KINGDOM
Bays, David, Ware, UNITED KINGDOM

PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)

PI US 6534486 B1 20030318
WO 9967266 19991229

AI US 2001-720193 20010228 (9)
WO 1999-EP4270 19990623

PRAI GB 1998-13535 19980623

DT Utility

FS GRANTED

EXNAM Primary Examiner: Wilson, James O.; Assistant Examiner: Lewis, Patrick T.

CLMN Number of Claims: 16

ECL Exemplary Claim: 1,14

DRWN 0 Drawing Figure(s); 0 Drawing Page(s)

LN.CNT 947

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 17 OF 28 USPATFULL on STN

AB There are provided according to the invention novel compounds of formula I ##STR1##

wherein R.sup.1, R.sup.2 and R.sup.3 are as described in the specification, processes for preparing them, formulations containing them and their use in therapy for the treatment of inflammatory diseases.

AN 2002:165221 USPATFULL

TI 2-(purin-9-yl)-tetrahydrofuran-3,4-diol derivatives

IN Cox, Brian, Stevenage, UNITED KINGDOM
Keeling, Suzanne Elaine, Stevenage, UNITED KINGDOM
Allen, David George, Stevenage, UNITED KINGDOM
Redgrave, Alison Judith, Stevenage, UNITED KINGDOM
Barker, Michael David, Stevenage, UNITED KINGDOM
Hobbs, Heather, Stevenage, UNITED KINGDOM
Roper, Thomas Davis, IV, Apex, NC, UNITED STATES
Geden, Joanna Victoria, London, UNITED KINGDOM

PI US 2002086850 A1 20020704
US 6528494 B2 20030304

AI US 2001-25678 A1 20011219 (10)

RLI Continuation of Ser. No. US 1999-331526, filed on 20 Aug 1999, PENDING A 371 of International Ser. No. WO 1997-EP7197, filed on 22 Dec 1997, UNKNOWN

PRAI GB 1996-26845 19961224
GB 1996-26852 19961224
GB 1996-26846 19961224
GB 1997-20536 19970927
GB 1997-22730 19971029

DT Utility

FS APPLICATION

LREP DAVID J LEVY, CORPORATE INTELLECTUAL PROPERTY, GLAXOSMITHKLINE, FIVE MOORE DR., PO BOX 13398, DURHAM, NC, 27709-3398

CLMN Number of Claims: 2

ECL Exemplary Claim: 1

DRWN No Drawings
LN.CNT 3228
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 18 OF 28 USPATFULL on STN
AB The present invention relates to the pulmonary administration of a therapeutic protein by means of powdered pharmaceutical compositions suitable for inhalation therapy. In particular the invention relates to dry powder formulations of secretory leukocyte protease inhibitor (SLPI) for pulmonary delivery. Exemplary pharmaceutical compositions contain SLPI and a pharmaceutically acceptable carrier in the form of a dry powder which is typically less than about 10% by weight water. About 50% to 95% by mass of the powder comprises particles or agglomerates of particles having a diameter within the range of from about 1.0 microns to about 8 microns, with a mass median diameter ranging from about 3.0 microns to about 6 microns.
AN 2002:17438 USPATFULL
TI Secretory leukocyte protease inhibitor dry powder pharmaceutical compositions
IN Niven, Ralph W., Redwood City, CA, UNITED STATES
Wright, Clifford D., Boulder, CO, UNITED STATES
Chang, Byeong S., Thousand Oaks, CA, UNITED STATES
PA Amgen, Inc. (U.S. corporation)
PI US 2002010318 A1 20020124
AI US 2001-896685 A1 20010629 (9)
RLI Continuation of Ser. No. US 1997-943759, filed on 3 Oct 1997, PENDING
DT Utility
FS APPLICATION
LREP AMGEN INCORPORATED, MAIL STOP 27-4-A, ONE AMGEN CENTER DRIVE, THOUSAND OAKS, CA, 91320-1799
CLMN Number of Claims: 25
ECL Exemplary Claim: 1
DRWN 12 Drawing Page(s)
LN.CNT 1992
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 19 OF 28 USPATFULL on STN
AB A series of 2-(Purin-9-yl)-tetrahydrofuran-3,4-diol derivatives with broad anti-inflammatory properties which inhibit leukocyte recruitment and activation and which are agonists of the adenosine 2a receptor are described.
AN 2002:332722 USPATFULL
TI 2-(Purin -9-yl)-tetrahydrofuran-3,4-diol derivatives
IN Allen, David George, Stevenage, UNITED KINGDOM
Chan, Chuen, Stevenage, UNITED KINGDOM
Cousins, Richard Peter Charles, Stevenage, UNITED KINGDOM
Cox, Brian, Stevenage, UNITED KINGDOM
Geden, Joanna Victoria, Aston Science Park, UNITED KINGDOM
Hobbs, Heather, Stevenage, UNITED KINGDOM
Keeling, Suzanne Elaine, Stevenage, UNITED KINGDOM
Redgrave, Alison Judith, Stevenage, UNITED KINGDOM
Roper, IV, Thomas Davis, Apex, NC, United States
Xie, Shiping, Cary, NC, United States
PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)
PI US 6495528 B1 20021217
WO 9967265 19991229
AI US 2001-720390 20010220 (9)
WO 1999-EP4269 19990623
PRAI GB 1998-13538 19980623
GB 1999-9482 19990423
DT Utility
FS GRANTED
EXNAM Primary Examiner: Wilson, James O.

CLMN Number of Claims: 26
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 1550
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 20 OF 28 USPATFULL on STN
AB There are provided according to the invention novel compounds of formula (I) wherein R.sup.1, R.sup.2, and R.sup.3 are as described in the specification, processes for preparing them, formulations containing them and their use in therapy for the treatment of inflammatory diseases.
AN 2002:188342 USPATFULL
TI 2-(Purin-9-yl)-tetrahydrofuran-3,4-diol derivatives
IN Cox, Brian, Stevenage, UNITED KINGDOM
Keeling, Suzanne Elaine, Stevenage, UNITED KINGDOM
Allen, David George, Stevenage, UNITED KINGDOM
Redgrave, Alison Judith, Stevenage, UNITED KINGDOM
Barker, Michael David, Stevenage, UNITED KINGDOM
Hobbs, Heather, Stevenage, UNITED KINGDOM
Roper, IV, Thomas Davis, Apex, NC, United States
Geden, Joanna Victoria, London, UNITED KINGDOM
PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)
PI US 6426337 B1 20020730
WO 9828319 19980702
AI US 1999-331526 19990820 (9)
WO 1997-EP7197 19971222
19990820 PCT 371 date
PRAI GB 1996-268453 19961224
GB 1996-268461 19961224
GB 1996-268529 19961224
GB 1997-205363 19970927
GB 1997-227300 19971029
DT Utility
FS GRANTED
EXNAM Primary Examiner: Wilson, James O.
LREP Rogers, Christopher P.
CLMN Number of Claims: 50
ECL Exemplary Claim: 1,14
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 3624
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 21 OF 28 USPATFULL on STN
AB The invention relates to a method of producing an agglomerate of drug and solid binder. The process involves producing individual agglomerate particles and then converting the convertible amorphous content of same, following agglomeration, by the application of, for example, moisture. Agglomerates capable of conversion as well as the finished agglomerates and oral and nasal dosing systems including same are also contemplated. The process produces agglomerates which are rugged but which will produce an acceptable fine particle fraction during dosing.
AN 2001:229238 USPATFULL
TI Preparation of powder agglomerates
IN Yang, Tsong-Toh, Warren, NJ, United States
PI US 2001051187 A1 20011213
US 6495167 B2 20021217
AI US 2001-901205 A1 20010709 (9)
RLI Continuation of Ser. No. US 2001-824377, filed on 2 Apr 2001, PENDING
Continuation of Ser. No. US 1998-42973, filed on 17 Mar 1998, ABANDONED
PRAI US 1997-41055P 19970320 (60)
DT Utility
FS APPLICATION

LREP SCHERING-PLOUGH CORPORATION, PATENT DEPARTMENT (K-6-1, 1990), 2000 GALLOPING HILL ROAD, KENILWORTH, NJ, 07033-0530
CLMN Number of Claims: 63
ECL Exemplary Claim: 1
DRWN 4 Drawing Page(s)
LN.CNT 1412
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 22 OF 28 USPATFULL on STN
AB Stabilized dispersions are provided for the delivery of a bioactive agent to the respiratory tract of a patient. The dispersions preferably comprise a plurality of perforated microstructures dispersed in a suspension medium that typically comprises a hydrofluoroalkane propellant. As density variations between the suspended particles and suspension medium are minimized and attractive forces between microstructures are attenuated, the disclosed dispersions are particularly resistant to degradation, such as, by settling or flocculation. In particularly preferred embodiments, the stabilized dispersions may be administered to the lung of a patient using a metered dose inhaler.
AN 2001:217988 USPATFULL
TI Stabilized preparations for use in metered dose inhalers
IN Weers, Jeffry G., San Diego, CA, United States
Schutt, Ernest G., San Diego, CA, United States
Dellamary, Luis A., San Marcos, CA, United States
Tarara, Thomas E., San Diego, CA, United States
Kabalnov, Alexey, Corvallis, OR, United States
PI US 2001046474 A1 20011129
US 6638495 B2 20031028
AI US 2001-862764 A1 20010521 (9)
RLI Division of Ser. No. US 1998-218212, filed on 22 Dec 1998, PENDING Continuation of Ser. No. WO 1998-US20615, filed on 29 Sep 1998, UNKNOWN Continuation-in-part of Ser. No. US 1998-133848, filed on 14 Aug 1998, ABANDONED Continuation-in-part of Ser. No. US 1998-106932, filed on 29 Jun 1998, ABANDONED
PRAI US 1997-60337P 19970929 (60)
DT Utility
FS APPLICATION
LREP INHALE THERAPEUTIC SYSTEMS, INC, 150 INDUSTRIAL ROAD, SAN CARLOS, CA, 94070
CLMN Number of Claims: 150
ECL Exemplary Claim: 1
DRWN 4 Drawing Page(s)
LN.CNT 2850
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 23 OF 28 USPATFULL on STN
AB The invention relates to a method of producing an agglomerate of drug and solid binder. The process involves producing individual agglomerate particles and then converting the convertible amorphous content of same, following agglomeration, by the application of, for example, moisture. Agglomerates capable of conversion as well as the finished agglomerates and oral and nasal dosing systems including same are also contemplated. The process produces agglomerates which are rugged but which will produce an acceptable fine particle fraction during dosing.
AN 2001:165431 USPATFULL
TI Preparation of powder agglomerates
IN Yang, Tsong-Toh, Warren, NJ, United States
PI US 2001024641 A1 20010927
US 6503537 B2 20030107
AI US 2001-824377 A1 20010402 (9)
RLI Continuation of Ser. No. US 1998-42973, filed on 17 Mar 1998, ABANDONED
PRAI US 1997-41055P 19970320 (60)
DT Utility

FS APPLICATION
LREP SCHERING-PLOUGH CORPORATION, PATENT DEPARTMENT (K-6-1, 1990), 2000 GALLOPING HILL ROAD, KENILWORTH, NJ, 07033-0530
CLMN Number of Claims: 63
ECL Exemplary Claim: 1
DRWN 4 Drawing Page(s)
LN.CNT 1413
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 24 OF 28 USPATFULL on STN
AB The present invention relates to the pulmonary administration of a therapeutic protein by means of powdered pharmaceutical compositions suitable for inhalation therapy. In particular the invention relates to dry powder formulations of secretory leukocyte protease inhibitor (SLPI) for pulmonary delivery. Exemplary pharmaceutical compositions contain SLPI and a pharmaceutically acceptable carrier in the form of a dry powder which is typically less than about 10% by weight water. About 50% to 95% by mass of the powder comprises particles or agglomerates of particles having a diameter within the range of from about 1.0 microns to about 8 microns, with a mass median diameter ranging from about 3.0 microns to about 6 microns.
AN 2001:105320 USPATFULL
TI SECRETORY LEUKOCYTE PROTEASE INHIBITOR DRY POWDER PHARMACEUTICAL COMPOSITIONS
IN NIVEN, RALPH W., REDWOOD CITY, CA, United States
WRIGHT, CLIFFORD D., BOULDER, CO, United States
CHANG, BYEONG S., THOUSAND OAKS, CA, United States
PI US 2001006939 A1 20010705
AI US 1997-943759 A1 19971003 (8)
DT Utility
FS APPLICATION
LREP AMGEN INCORPORATED, MAIL STOP 27-4-A, ONE AMGEN CENTER DRIVE, THOUSAND OAKS, CA, 91320-1799
CLMN Number of Claims: 25
ECL Exemplary Claim: 1
DRWN 12 Drawing Page(s)
LN.CNT 1989
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 25 OF 28 USPATFULL on STN
AB Stabilized dispersions are provided for the delivery of a bioactive agent to the respiratory tract of a patient. The dispersions preferably comprise a plurality of perforated microstructures dispersed in a suspension medium that typically comprises a hydrofluoroalkane propellant. As density variations between the suspended particles and suspension medium are minimized and attractive forces between microstructures are attenuated, the disclosed dispersions are particularly resistant to degradation, such as, by settling or flocculation. In particularly preferred embodiments, the stabilized dispersions may be administered to the lung of a patient using a metered dose inhaler.
AN 2001:190709 USPATFULL
TI Stabilized preparations for use in metered dose inhalers
IN Weers, Jeffry G., San Diego, CA, United States
Schutt, Ernest G., San Diego, CA, United States
Dellamary, Luis A., San Marcos, CA, United States
Tarara, Thomas E., San Diego, CA, United States
Kabalnov, Alexey, Corvallis, OR, United States
PA Inhale Therapeutic Systems, Inc., San Carlos, CA, United States (U.S. corporation)
PI US 6309623 B1 20011030
AI US 1998-218212 19981222 (9)
RLI Continuation of Ser. No. WO 1998-US20615, filed on 29 Sep 1998
Continuation-in-part of Ser. No. US 1998-133848, filed on 14 Aug 1998,

now abandoned Continuation-in-part of Ser. No. US 1998-106932, filed on 29 Jun 1998, now abandoned
PRAI US 1997-60337P 19970929 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Bawa, Raj
LREP Rafa, Michael J., Cagan, Felissa H.
CLMN Number of Claims: 93
ECL Exemplary Claim: 1
DRWN 17 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 2644
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 26 OF 28 USPATFULL on STN
AB A medicament carrier (10) having a first and a second spaced apart screen (12, 14) each of which has surfaces (12B, 14B) defining a plurality of interstices (12A, 14A). The carrier (10) contains powdered agglomerated medicament particles (SM) loaded onto the first screen surface (12B) such that the interstices (12A) of the first screen (12) are at least partially open and free of the agglomerated medicament particles (SM). When an air stream is provided to the carrier to entrain the agglomerated powdered medicament particles (SM) and move them from the first screen (12) through the interstices (14A) of the second screen (14), the agglomerated powdered medicament particles (SM) are sheared by air flow gradients created by the first and second screens (12, 14) and by contact with the surface (14B) of the second screen (14) to create particles of respirable particle size range. The carrier (10) can be used in a dry powder inhalator device.
AN 2001:86043 USPATFULL
TI Medicament carrier with agglomerated large medicament particles and related method of manufacture thereof
IN Van Oort, Michiel Mary, Durham, NC, United States
Sacchetti, Mark Joseph, Raleigh, NC, United States
PA Glaxo Wellcome Inc., Research Triangle Park, NC, United States (U.S. corporation)
PI US 6245339 B1 20010612
WO 9804308 19980205
AI US 1999-230613 19990128 (9)
WO 1997-EP4128 19970730
19990128 PCT 371 date
19990128 PCT 102(e) date
PRAI GB 1996-16047 19960731
DT Utility
FS GRANTED
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Ware, Todd D.
LREP Riek, James P.
CLMN Number of Claims: 35
ECL Exemplary Claim: 1
DRWN 9 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 938

L9 ANSWER 27 OF 28 USPATFULL on STN
AB Pharmaceutical compositions comprising effective amounts of salmeterol (and/or a physiologically acceptable salt thereof) and fluticasone propionate as a combined preparation for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorders.
AN 93:104950 USPATFULL
TI Medicaments
IN Palmer, James B. D., Greenford, United Kingdom
PA Glaxo Group Limited, London, United Kingdom (non-U.S. corporation)
PI US 5270305 19931214
AI US 1991-753907 19910903 (7)
DCD 20100504

RLI Continuation of Ser. No. US 1990-578601, filed on 7 Sep 1990, now abandoned
PRAI GB 1989-20392 19890908
GB 1989-23644 19891020
DT Utility
FS Granted
EXNAM Primary Examiner: Rose, Shep K.
LREP Bacon & Thomas
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 306
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 28 OF 28 USPATFULL on STN
AB Pharmaceutical compositions comprising effective amounts of salmeterol (and/or a physiologically acceptable salt thereof) and **beclomethasone dipropionate** as a combined preparation for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorders.
AN 93:35676 USPATFULL
TI Medicaments
IN Palmer, James B. D., Greenford, United Kingdom
PA Glaxo Group Limited, London, England (non-U.S. corporation)
PI US 5208226 19930504
AI US 1991-753906 19910903 (7)
RLI Continuation of Ser. No. US 1990-578606, filed on 7 Sep 1990, now abandoned
PRAI GB 1989-20391 19890908
GB 1989-23645 19891020
DT Utility
FS Granted
EXNAM Primary Examiner: Rose, Shep K.
LREP Bacon & Thomas
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 300
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d 1-28 kwic

L9 ANSWER 1 OF 28 USPATFULL on STN
SUMM . . . of treating diseases and conditions of the upper and lower airway passages and the lungs. These conditions include, for example, **asthma** and rhinitis. One such technique involves administering certain pharmacologically active agents or drugs such as, for example, mometasone furoate, topically. . .
SUMM . . . when administering OTC nasal sprays, variation should be minimized where possible when administering prescription medications for such serious conditions as **asthma**. The dangers of over-medicating or under-medicating and the consequences of such unwanted deviation can be profound. The problem becomes even. . .
DETD . . . topically. Particularly preferred pharmacologically active agents in accordance with the present invention include, without limitation, corticosteroids such as: mometasone furoate; **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; (22R)-6.alpha.,9.alpha.-difluoro-11.beta.,21-dihydroxy-16.alpha.,17.alpha.-propylmethylenedioxy-4-pregnen-3,20-dione; tipredane and the like. .beta.-agonists (including .beta..sub.1 and .beta..sub.2-agonists) including, without limitation, **salbutamol** (albuterol), terbutaline, salmeterol, and bitolterol may also be administered. Formoterol (also known as eformoterol) e.g.,

as the fumarate or tartrate,. . .

DETD . . . results. Such inhalers include, without limitation, Schering's inhaler as identified above, Diskhaler (Allen & Hanburys), Accuhaler (Allen & Hanburys), Diskus (**Glaxo**), Spiros (Dura), Easyhaler (Orion), Cyclohaler (Pharmachemie), Cyclovent (Pharmachemie), Rotahaler (**Glaxo**), Spinhaler (Fisons), FlowCaps(Hovione), Turbospin (PH&T), Turbohaler (Astra), EZ Breath (Norton Healthcare/IVAX), MIAT-HALER (Miat), Pulvinal (Chiesi), Ultrahaler (Fisons/ Rhone Poulenc Rorer),. . .

CLM What is claimed is:

. . . claim 2, wherein said pharmacologically active agent comprises at least one member selected from the group consisting of: mometasone furoate; **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; **salbutamol**; albuterol; terbutaline; salmeterol; bitolterol; ipratropium bromide; oxitropium bromide; sodium cromoglycate; nedocromil sodium; zafirlukast; pranlukast; formoterol; eformoterol; bambuterol; fenoterol; clenbuterol; procaterol;. . .

. . . claim 46, wherein said pharmacologically active agent comprises at least one member selected from the group consisting of: mometasone furoate; **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; **salbutamol**; albuterol; terbutaline; salmeterol; bitolterol; ipratropium bromide; oxitropium bromide; sodium cromoglycate; nedocromil sodium; zafirlukast; pranlukast; formoterol; eformoterol; bambuterol; fenoterol; clenbuterol; procaterol;. . .

. . . claim 53, wherein said pharmacologically active agent comprises at least one member selected from the group consisting of: mometasone furoate; **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; **salbutamol**; albuterol; terbutaline; salmeterol; bitolterol; ipratropium bromide; oxitropium bromide; sodium cromoglycate; nedocromil sodium; zafirlukast; pranlukast; formoterol; eformoterol; bambuterol; fenoterol; clenbuterol; procaterol;. . .

L9 ANSWER 2 OF 28 USPATFULL on STN

SUMM [0008] International Patent Application No. WO 92/08446 (**Glaxo** Group Limited) and EP-A-0 493437 (Riker Laboratories Inc) disclose the presence of surfactants in pharmaceutical aerosol formulations, however, the use of lactose or other sugars is not described. WO 94/03153 (**Glaxo** Group Limited) discloses a suspension formulation of **beclomethasone dipropionate**, but specifically excludes the presence of a surfactant. WO 93/11743, WO 93/11744 and WO 93/11745 (**Glaxo** Group Limited) also disclose suspension formulations of drugs which specifically exclude the presence of surfactant. WO 97/35562 (Danbiosyst) describes the. . .

SUMM [0019] These therapeutic agents encompass in particular bronchodilators and steroidal antiinflammatories commonly used in the treatment of **asthma**, such as **beclomethasone dipropionate**, **salbutamol** (eg as sulphate or free base), salmeterol (eg as 1-hydroxy-2-naphthoate salt), fluticasone propionate or solvates thereof. Other compounds of interest. . .

SUMM [0020] Among these, use is preferably made of **beclomethasone dipropionate** and in particular of its monohydrate. Use in relation to salmeterol xinafoate is also preferred.

DETD . . . lecithin are dissolved in 100 ml of demineralized water at room temperature. After obtaining a colloidal solution, 5 g of **beclomethasone dipropionate** monohydrate (BDP) as micronised particles are dispersed with stirring in the aqueous solution. The suspension thus obtained contains 5% BDP,. . .

DETD . . . lecithin are dissolved in 100 ml of demineralized water at room temperature. After obtaining a colloidal solution, 5 g of **beclomethasone dipropionate** monohydrate (BDP) as micronised particles are dispersed with stirring in the aqueous

solution. The suspension thus obtained contains 5% BDP,. . .

DETD [0098] 20 g of micronised particles of **beclomethasone dipropionate** monohydrate are triturated with 1 g of lecithin in a mortar until a homogeneous physical mixture is obtained. 2 g. . .

DETD . . . lecithin are dissolved in 100 ml of demineralized water at room temperature. After obtaining a colloidal solution, 20 g of **beclomethasone dipropionate** monohydrate (BDP) as micronised particles are dispersed with stirring in the aqueous solution. The suspension thus obtained contains 20% BDP,. . .

DETD [0125] 2 g of lecithin are dissolved in 100 ml of demineralized water at room temperature. 20 g of **beclomethasone dipropionate** monohydrate are pre-mixed with 2 g of lactose and the blend dispersed under stirring in the lecithin aqueous solution.

DETD . . . g of lecithin are dissolved in 1000 ml of demineralized water at room temperature (20.degree. C..+-.2.degree. C.). 150 g of **beclomethasone dipropionate** monohydrate are pre-mixed with 15 g of lactose and the blend dispersed under stirring in the lecithin aqueous solution.

DETD . . . g of lecithin are dissolved in 1500 ml of demineralized water at room temperature (20.degree. C..+-.2.degree. C.). 225 g of **beclomethasone dipropionate** monohydrate are pre-mixed with 22.5 g of lactose and the blend is dispersed under stirring in the lecithin aqueous solution.

DETD . . . of lecithin are dissolved in 1500 ml of demineralized water at room temperature (20.degree. C. .+-.2.degree. C.). 225 g of **beclomethasone dipropionate** monohydrate are pre-mixed with 22.5 g of lactose and the blend is dispersed under stirring in the lecithin aqueous solution.

DETD . . . g of lecithin are dissolved in 2000 ml of demineralized water at room temperature (20.degree. C..+-.2.degree. C.). 300 g of **beclomethasone dipropionate** monohydrate are pre-mixed with 30 g of lactose and the blend dispersed under stirring in the lecithin aqueous solution.

DETD . . . g of lecithin are dissolved in 2000 ml of demineralized water at room temperature (20.degree. C..+-.2.degree. C.). 300 g of **beclomethasone dipropionate** monohydrate are pre-mixed with 30 g of lactose and the blend dispersed under stirring in the lecithin aqueous solution.

DETD . . . g of lecithin are dissolved in 1000 ml of demineralized water at room temperature (20.degree. C..+-.2.degree. C.). 150 g of **beclomethasone dipropionate** monohydrate are pre-mixed with 15 g of lactose and the blend dispersed under stirring in the lecithin aqueous solution.

DETD . . . g of lecithin are dissolved in 2000 ml of demineralized water at room temperature (20.degree. C..+-.2.degree. C.). 150 g of **beclomethasone dipropionate** monohydrate are pre-mixed with 30 g of lactose and the blend dispersed under stirring in the lecithin aqueous solution.

DETD . . . g of lecithin are dissolved in 2000 ml of demineralized water at room temperature (20.degree. C..+-.2.degree. C.). 300 g of **beclomethasone dipropionate** monohydrate are pre-mixed with 30 g of lactose and the blend dispersed under stirring in the lecithin aqueous solution.

CLM What is claimed is:

3. A pharmaceutical aerosol formulation according to claim 2, characterised in that the therapeutic agent is chosen from **beclomethasone dipropionate**, **salbutamol** (eg as sulphate or free base), salmeterol (eg as 1-hydroxy-2-naphoate salt), fluticasone propionate or solvates thereof.

4. A pharmaceutical aerosol formulation according to claim 3, characterised in that the therapeutic agent is **beclomethasone dipropionate** or a solvate thereof, in particular **beclomethasone dipropionate** monohydrate.

40. Particles according to claim 39 wherein the therapeutic agent is **beclomethasone dipropionate** or a solvate thereof, the suspending medium is water, the coating excipient is lactose and the surfactant is lecithin.

L9 ANSWER 3 OF 28 USPATFULL on STN

SUMM . . . i.e. (1.alpha.,2.beta.,4.beta.,5.alpha.,7.beta.)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.2.0]nonane and particularly its bromide salt is a well-known anti-cholinergic agent, described in EP418,716 for the treatment of bronchial **asthma** and related disorders.

SUMM [0004] Although tiotropium bromide and mometasone may be effective therapies, there exists a clinical need for **asthma** therapies having potent and selective action and having an advantageous profile of action.

SUMM . . . an anticholinergic agent and/or an antiinflammatory corticosteroid is indicated. Such conditions include diseases associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

SUMM . . . present invention provides such methods for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . aspect, the invention is concerned with the prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . to the invention may further include other therapeutic agents for example anti-inflammatory agents such as other corticosteroids (e.g. fluticasone propionate, **beclomethasone dipropionate**, budenoside, or triamcinolone acetonide), or NSAIDs (e.g. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists), or .beta..sub.2-adrenoreceptor agonists (such as **salbutamol**, salmeterol, formoterol, fenoterol or terbutaline and salts thereof, or other anticholinergic agents (such as ipratropium).

DETD . . . be administered by an inhaler such as a Rotahaler, Diskhaler, or Diskus inhaler (each of these being a Trademark of **Glaxo** Group Limited).

CLM What is claimed is:

. . . A method according to claim 7 wherein the clinical condition is a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

L9 ANSWER 4 OF 28 USPATFULL on STN

SUMM . . . compounds which are .beta..sub.2-adrenoreceptor agonists including 4-hydroxy-.alpha..sup.1-[[[6-(4-phenylbutoxy)hexyl]-amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of bronchial **asthma** and related disorders.

SUMM . . . thereof and pharmaceutical formulations thereof. Budesonide is an antiinflammatory corticosteroid, which is now used clinically in the treatment of bronchial **asthma** and related disorders.

SUMM [0004] Although salmeterol xinafoate and budesonide are effective therapies, there exists a clinical need for **asthma** therapies having potent and selective action and having an advantageous profile of action.

SUMM . . . selective .beta..sub.2-adrenoreceptor agonist and/or an antiinflammatory corticosteroid is indicated. Such conditions include diseases associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

SUMM . . . present invention provides such methods for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . aspect, the invention is concerned with the prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . to the invention may further include other therapeutic agents for example anti-inflammatory agents such as other corticosteroids (e.g. fluticasone propionate, **beclomethasone dipropionate**, mometasone furoate, or triamcinolone acetonide), or NSAIDs (e.g. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists), or other .beta..sub.2-adrenoreceptor agonists (such as **salbutamol**, formoterol, fenoterol or terbutaline and salts thereof, or anticholinergic agents (such as ipratropium, or tiotropium).

DETD . . . ~~be administered by an inhaler such as a Rotahaler, Diskhaler,~~ or Diskus inhaler (each of these being a Trademark of **Glaxo** Group Limited).

CLM What is claimed is:

. . . A method according to claim 6 wherein the clinical condition is a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

L9 ANSWER 5 OF 28 USPATFULL on STN

SUMM . . . 5.alpha., 7.beta.)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.2.0]nonane and particularly its bromide salt is a well-known anti-cholinergic agent, described in EP418,716 for the treatment of bronchial **asthma** and related disorders.

SUMM . . . thereof and pharmaceutical formulations thereof. Rofleponide is an antiinflammatory corticosteroid, which is proposed for use in the treatment of bronchial **asthma** and related disorders.

SUMM [0004] Although tiotropium bromide and rofleponide may be effective therapies, there exists a clinical need for **asthma** therapies having potent and selective action and having an advantageous profile of action.

SUMM . . . which anticholinergic agent and/or an antiinflammatory corticosteroid is indicated. Such conditions include diseases associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

SUMM . . . present invention provides such methods for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . aspect, the invention is concerned with the prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . to the invention may further include other therapeutic agents for example anti-inflammatory agents such as other corticosteroids (e.g. fluticasone propionate, **beclomethasone dipropionate**,

mometasone furoate, triamcinolone acetonide or budesonide) or NSAIDs (e.g. sodium cromoglycate, nedocromil sodium; PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists), or, .beta..sub.2-adrenoreceptor agonists (such as **salbutamol**, formoterol, salmeterol, fenoterol or terbutaline and salts thereof), or other anticholinergic agents (such as ipratropium).

DETD . . . be administered by an inhaler such as a Rotahaler, Diskhaler, or Diskus inhaler (each of these being a Trademark of **Glaxo** Group Limited).

CLM What is claimed is:

. . . A method according to claim 7 wherein the clinical condition is a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

L9 ANSWER 6 OF 28 USPATFULL on STN

SUMM . . . i.e. (1.alpha.,2.beta.,4.beta.,5.alpha.,7.beta.)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.2.0]nonane and particularly its bromide salt is a well-known anti-cholinergic agent, described in EP418,716 for the treatment of bronchial **asthma** and related disorders.

SUMM . . . thereof and pharmaceutical formulations thereof. Budesonide is an antiinflammatory corticosteroid, which is now used clinically in the treatment of bronchial **asthma** and related disorders.

SUMM [0004] Although tiotropium bromide and budesonide are effective therapies, there exists a clinical need for **asthma** therapies having potent and selective action and having an advantageous profile of action.

SUMM . . . an anticholinergic agent and/or an antiinflammatory corticosteroid is indicated. Such conditions include diseases associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

SUMM . . . present invention provides such methods for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . aspect, the invention is concerned with the prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . to the invention may further include other therapeutic agents for example anti-inflammatory agents such as other corticosteroids (e.g. fluticasone propionate, **beclomethasone dipropionate**, mometasone furoate, or triamcinolone acetonide) or NSAIDs (e.g. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, INOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists), or .beta..sub.2-adrenoreceptor agonists (such as **salbutamol**, salmeterol, formoterol, fenoterol or terbutaline and salts thereof), or other anticholinergic agents (such as ipratropium).

DETD . . . be administered by an inhaler such as a Rotahaler, Diskhaler, or Diskus inhaler (each of these being. a Trademark of **Glaxo** Group Limited).

CLM What is claimed is:

. . . A method according to claim 6 wherein the clinical condition is a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

L9 ANSWER 7 OF 28 USPATFULL on STN

AB Elongated drug, especially **salbutamol** sulphate, and/or carrier particles, especially lactose, pharmaceutical compositions comprising the same, and use of the elongated particles in the manufacture. . .

SUMM [0002] Numerous medicaments, especially those for the treatment of respiratory conditions such as **asthma**, are administered by inhalation. Since the drug acts directly on the target organ much smaller quantities of the active ingredient. . .

SUMM . . . triamcinolone acetonide or fluticasone; antitussives, e.g. noscapine; bronchodilators, e.g. ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephnine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, **salbutamol**, salmeterol, terbutalin; isoetharine, tulobuterol, orciprenaline or (-)-4-amino-3,5-dichloro-.alpha.-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]-amino]methyl]benzenemethanol; diuretics, e.g. amiloride; anticholinergics, e.g. ipratropium, atropine or oxitropium; hormones, e.g. cortisone, hydrocortisone. . .

SUMM . . . accordance with the invention include anti-allergics, bronchodilators and anti-inflammatory steroids of use in the treatment of respiratory disorders such as **asthma** by inhalation therapy, for example cromoglycate (e.g. as the sodium salt), **salbutamol** (e.g. as the free base or as the sulphate salt), salmeterol (e.g. as the xinafoate salt), terbutaline (e.g. as the sulphate salt), reproterol (e.g. as the hydrochloride salt), **beclomethasone dipropionate** (e.g. as the monohydrate), fluticasone propionate or (-)-4-amino-3,5-dichloro-.alpha.-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol. Salmeterol, **salbutamol**, fluticasone propionate, **beclomethasone dipropionate**, ipratropium and physiologically acceptable salts and solvates thereof are especially preferred.

SUMM [0016] Other powder compositions may contain bronchodilators such as **salbutamol** (e.g. as the free base or as the sulphate salt), salmeterol (e.g. as the xinafoate salt) or isoprenaline in combination. . . an antiallergic such as cromoglycate (e.g. the sodium salt). Combinations of isoprenaline and sodium cromoglycate, salmeterol and fluticasone propionate, or **salbutamol** and **beclomethasone dipropionate** are especially preferred.

SUMM [0024] For example, elongated **salbutamol** sulphate crystals may be prepared by adding an aqueous solution of **salbutamol** sulphate to absolute ethanol.

SUMM [0050] Thus, for example, each actuation may deliver 25 micrograms salmeterol, 100 micrograms **salbutamol**, 25, 50, 125 or 250 micrograms fluticasone propionate or 50, 100, 200 or 250 micrograms **beclomethasone dipropionate**.

DETD Deposition Profiles of **Salbutamol** Sulphate From Different Batches of Lactose Crystals

DETD [0066] **Salbutamol** sulphate and lactose were mixed in a ratio of 1:67.5, w/w in accordance with the ratio employed in the commercial "Ventolin.TM." formulation. After drying in a vacuum over at 400.degree. C. for 12 h, micronised **salbutamol** sulphate with mass median diameter 2.0 .mu.m (**Glaxo** Wellcome Group Ltd., Ware, UK) (25 mg), was weighed into a 10 ml stoppered sample vial to which had been. . . Whirlymixer for another 5 s. This process was repeated until all the lactose (1.750 g) had been incorporated into the **salbutamol** sulphate/lactose blend to obtain a ratio of drug to carrier of 1:67.5, w/w. The stoppered vials were then placed in. . .

DETD . . . Ten samples were taken randomly from each batch. The sample (approximately 33 mg) was weighed accurately and the amount of **salbutamol** sulphate was measured by HPLC. The coefficient of variation of the drug content was employed to assess the homogeneity of. . .

DETD [0068] Hard gelatin capsules (Size 3, Rotacapsule.TM., **Glaxo** Wellcome Group Ltd., Ware, UK) were filled with 33.0.+-.1.5 mg of the powder mixture so that each capsule contains 481.+-.22 .mu.g

salbutamol sulphate, which was the unit dose contained in a Ventolin Rotacap.TM.. The filling was performed manually.

DETD . . . dissolved in the internal standard solution, and made up to volume to obtain a concentration of 0.2 mg ml.sup.-1 of **salbutamol** sulphate (solution A). 10.0 ml of solution A was pipetted into another 100 ml volumetric flask and diluted to volume with the internal standard solution to obtain a solution containing 20 .mu.g ml.sup.-1 **salbutamol** sulphate (solution B).

DETD . . . .mu.l of the filtrate was injected into the HPLC. No interference from the lactose carrier was observed. The concentration of **salbutamol** sulphate was calculated by interpolation using the previously constructed calibration curve.

DETD . . . of a twin stage liquid impinger. The capsule, to be tested, was placed in a commercially available inhaler (either Rotahaler.TM., **Glaxo** Wellcome, Ware, UK or Cyclohaler.TM., Pharbita BV, the Netherlands), which had been fitted into a moulded rubber mouthpiece attached to. . . both the upper and the lower stage of the twin-impinger. All the samples obtained were analysed for the concentration of **salbutamol** sulphate using HPLC.

DETD . . . drug was assessed by the ratio of the recovered dose to the theoretical dose, the latter being the dose of **salbutamol** sulphate in the capsules. For example, the theoretical dose of **salbutamol** sulphate in one capsule was 481.+-.22 .mu.g, which was equivalent to the filling weight (33.0.+-.1.5 mg) of lactose and **salbutamol** sulphate blends.

DETD [0075] The mixtures were found to be homogenous with a coefficient of variation in **salbutamol** sulphate content of less than 2.2% (n=10).

DETD . . . capsule per actuation at 60 l min.sup.-1 via a Cyclohaler.TM.. It can be seen that the recovered dose (RD) of **salbutamol** sulphate varied from 391 .mu.g for the blend containing batch 9 lactose to 508 .mu.g for the blend composed of. . .

DETD [0077] The blends containing batch 9, 10, 11 and Lactochem.TM. lactose produced a similar fine particle dose (FPD) of **salbutamol** sulphate, which was significantly higher ($p<0.01$) than that obtained from the blends which were composed of batch 3, 4 or. . . for the differences in the deposition of the drug since all the powders are composed of the same batch of **salbutamol** sulphate. The lowest values for FPF of drug, obtained using blends containing batch 3 or 4 lactose may be due to those batches having the roughest surfaces with the least elongated particle shape.

TABLE 6

Deposition of **salbutamol** sulphate from different batches of lactose in a twin-impinger after aerosolisation at 60 l min.sup.-1 via a Cyclohaler .TM. [mean (SD), n. . .

DETD . . . smoothness of lactose carrier particles, as expressed by the "surface factor", generally resulted in an increase in the FPF of **salbutamol** sulphate in terms of either % RD or % ED. Interestingly, increasing the elongation ratio of the lactose carrier particles also resulted in an increase in the FPF of **salbutamol** sulphate (FIG. 4.3). These results show that apart from surface smoothness, the elongation of carrier particles may also play an. . .

DETD Elongated **Salbutamol** Crystals Prepared by Recrystallisation

DETD [0080] **Salbutamol** sulphate was crystallised by adding its aqueous solution to absolute ethanol to obtain elongated crystals (needle shaped) of **salbutamol** sulphate having a mass median diameter of 5.49 .mu.m.

DETD [0081] After blending with Lactochem.TM. lactose, the recrystallised **salbutamol** sulphate gave a fine particle fraction (<6.4 .mu.m) of 22.8% recovered dose, which was more than double the fine particle fraction (10.8% recovered dose) of micronised **salbutamol**

sulphate with a mass median diameter of 4.79 .mu.m.

DETD [0086] **Salbutamol** sulphate (Allchem International, Maidenhead, UK) and lactose were mixed in a ratio of 1:67.5 w/w in accordance with the ratio employed in commercial Ventolin Rotacaps.TM.. Stoppered vials, containing the separate blends of **salbutamol** sulphate with lactose, were placed in a Turbula mixer (Glen Greston Ltd., Middx, UK) and mixing was carried out for. . .

DETD [0087] Deposition of **salbutamol** sulphate from each blend was determined using a twin-impinger after aerosolisation of 3 capsules at 60 l min.sup.-1 via a. . . lower stage of a twin stage liquid impinger. The capsule to be tested was placed in the inhaler device (Rotahaler.TM., **Glaxo** Wellcome, Ware, UK) which had been fitted into a moulded rubber mouthpiece attached to the throat piece of the impinger.. . . were washed individually and made up to volume (100 ml). All the samples obtained were analysed for the concentration of **salbutamol** sulphate.

DETD [0088] Deposition of **salbutamol** sulphate from each formulation was determined at least 5 times and a variety of parameters were employed to characterised the. . .

DETD [0089] Table 8 shows the percentage recoveries and coefficient of variation (CV) in **salbutamol** sulphate content obtained for both formulations. It can be seen that both formulations showed a recovery of **salbutamol** sulphate close to 100% with CV less than 2%. These suggest that the overall process of mixing, sampling and analysis. . . . a uniform mixing was achieved using the mixing procedure as described above.

TABLE 8

Recovery and coefficient of variation (CV) in **salbutamol** sulphate content obtained from the formulations containing Lactose crystals and Needle-shaped lactose crystals (n = 10).

	Lactose crystals	Needle-shaped lactose crystals
% Recovery. . .		

DETD . . . Powder formulations containing Lactose crystals and needle-shaped lactose as the carrier were shown to produce differences in the deposition of **salbutamol** sulphate (Tables 9 & 10). The recovered doses (RD) of **salbutamol** sulphate were similar for both formulations, corresponding to a percentage recovery of 93%. There was also no marked difference in. . .

DETD . . . of the drug in comparison to Lactose Crystals.

TABLE 9

Recovered dose (RD), emitted dose (ED) and fine particle dose (FPD) of **salbutamol** sulphate using Lactose crystals and Needle-shaped lactose (Mean .+-. SD, n = 5).

Carrier (63-90 .mu.m)	RD	ED	FPD
Lactose Crystals	458.6 .+-.. . .		

DETD [0092]

TABLE 10

Fine particle fraction, dispersibility, percentage recovery and percentage emission of **salbutamol** sulphate using lactose crystals and needle-shape lactose crystals (mean .+-. SD, n = 5).

Carrier (63-90 .mu.m)	FPF	Dispersibility	% Recovery	%. . .

DETD [0093] The incorporation of needle-shaped lactose produced at least 4 times the fine particle fraction and dose of **salbutamol** sulphate than of the formulation containing commercial grade of lactose. Therefore, the use of needle lactose has a huge potential. . .

DETD [0098] **Salbutamol** sulphate and lactose were mixed in a ratio of 1:67.5 w/w as described in Example 8.

DETD [0099] Deposition of **salbutamol** sulphate from each blend was determined as described in Example 8.

DETD [0100] Table 12 shows the percentage recoveries and coefficient of variation (CV) in **salbutamol** sulphate content obtained for both formulations. It can be seen that the recovery of **salbutamol** sulphate is quite similar for both formulations with CV less than 3%. These suggest that the overall process of mixing,. . . uniform mixing was achieved using the mixing procedure as described above.

TABLE 12

% Recovery and coefficient of variation (CV) in **salbutamol** sulphate content obtained from the formulations containing Lactose crystals and recrystallised lactose obtained from 80% acetone: 20% lactose solution. (n = 10).

Lactose. . .

DETD . . . Powder formulations containing Lactose crystals and recrystallised lactose as the carrier were shown to produce differences in the deposition of **salbutamol** sulphate (Tables 13 & 14). The recovered doses (RD) of **salbutamol** sulphate were similar for both formulations, corresponding to a percentage recovery of ~~93.5%.+-.3.1 and 99.4.+-.5.8 of **salbutamol** sulphate using~~ lactose crystals and recrystallised lactose as a carrier respectively. Recrystallised lactose produced higher dispersibility and better emission of **salbutamol** sulphate from inhaler device than lactose crystals (Table 14). These suggest that recrystallised lactose has a great potential in improving the dispersion and deaggregation of **salbutamol** sulphate.

DETD . . . of the drug in comparison to Lactose Crystals.

TABLE 13

Recovered dose (RD), emitted dose (ED) and final particle dose (FPD) of **salbutamol** sulphate using Lactose crystals and recrystallised lactose (80% acetone: 20% lactose solution). (Mean .+-. SD, n = 5).

Lactose (63-90 .mu.m) RD ED. . .

DETD [0103]

TABLE 14

Fine particle fraction, dispersibility, percentage recovery and percentage emission of **salbutamol** sulphate using lactose crystals and recrystallised lactose crystals (mean .+-. SD, n = 5).

Lactose
(63-90 .mu.m) FPF Dispersibility % Recovery %. . .

CLM What is claimed is:

3. Drug as claimed in claim 1 or 2, wherein the drug is salmeterol, **salbutamol**, fluticasone propionate, **beclomethasone dipropionate**, formoterol, budesonide, ipratropium, oxitropium or a physiologically acceptable salt or solvate thereof.

4. Drug as claimed in claim 3, wherein the drug is salmeterol, **salbutamol**, fluticasone propionate, or **beclomethasone dipropionate** or a physiologically acceptable salt or solvate thereof.

11. Use as claimed in claim 9 or 10, wherein the drug is salmeterol, **salbutamol**, fluticasone propionate, **beclomethasone dipropionate**, formoterol, budesonide, ipratropium, oxitropium or a physiologically acceptable salt or solvate thereof.

12. Use as claimed in claim 11, wherein the drug is salmeterol, **salbutamol**, fluticasone propionate, or **beclomethasone dipropionate** or a physiologically acceptable salt or solvate thereof.

19. A pharmaceutical composition as claimed in claim 17 or 18, wherein the drug is salmeterol, **salbutamol**, fluticasone propionate, **beclomethasone dipropionate**, formoterol, budesonide, ipratropium, oxitropium or a physiologically acceptable salt or solvate thereof.

20. A pharmaceutical composition as claimed in claim 19, wherein the drug is salmeterol, **salbutamol**, fluticasone propionate, or **beclomethasone dipropionate** or a physiologically acceptable salt or solvate thereof.

25. **Salbutamol** sulphate having a mean median diameter of 5.49 .mu.m obtained by adding an aqueous solution of **salbutamol** sulphate to absolute ethanol and collecting the crystals.

26. Use of **salbutamol** sulphate as claimed in claim 25 in the manufacture of a medicament for the treatment of respiratory disease, wherein the. . .

~~27. A pharmaceutical composition comprising **salbutamol**~~ sulphate as claimed in claim 25 and/or carrier particles wherein the composition in use in an inhalation device has a. . .

L9 ANSWER 8 OF 28 USPATFULL on STN

SUMM . . . compounds which are .beta..sub.2-adrenoreceptor agonists including 4-hydroxy-.alpha..sup.1-[[[6-(4-phenylbutoxy)hexyl]-amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of bronchial **asthma** and related disorders.

SUMM [0004] Although salmeterol xinafoate and mometasone furoate are effective therapies, there exists a clinical need for **asthma** therapies having potent and selective action and having an advantageous profile of action.

SUMM . . . selective .beta..sub.2-adrenoreceptor agonist and/or an antiinflammatory corticosteroid is indicated. Such conditions include diseases associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

SUMM . . . present invention provides such methods for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . aspect, the invention is concerned with the prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . to the invention may further include other therapeutic agents for example anti-inflammatory agents such as other corticosteroids (e.g. fluticasone propionate, **beclomethasone dipropionate**, budenoside, or triamcinolone acetonide), or NSAIDs (e.g. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists), or other .beta..sub.2-adrenoreceptor agonists (such as **salbutamol**, formoterol, fenoterol or terbutaline and salts thereof), or anticholinergic agents (such as ipratropium, or tiotropium).

DETD . . . be administered by an inhaler such as a Rotahaler, Diskhaler, or Diskus inhaler (each of these being a Trademark of **Glaxo**

Group Limited). Similar methods may be used for the formulations of Example 6:

Example 6

Per cartridge or blister

Salmeterol. . .

DETD . . . The blend was then filled into specifically constructed double foil blister packs to be administered by a Diskhaler (Trademark of **Glaxo** Group Limited).

C: Suspension for nebulisation

Example 8

	Quantity (mg)
Salmeterol Xinafoate (micronised)	0.0725
Mometasone Furoate (micronised)	0.20
Polysorbate 20. . .	

CLM What is claimed is:

. . . A method according to claim 6 wherein the clinical condition is a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

L9 ANSWER 9 OF 28 USPATFULL on STN

SUMM . . . i.e. (1.alpha.,2.beta.,4.beta.,5.alpha.,7.beta.)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.2.0]nonane and particularly its bromide salt is a well-known anti-cholinergic agent, described in EP418,716 for the treatment of bronchial **asthma** and related disorders.

SUMM . . . in GB 2088877, and is systematically named S-fluoromethyl-6a, 9a-difluoro-11.beta.-hydroxy-16.alpha.-methyl-17.alpha.-propionyloxy-3-oxoandrosta-1,4-diene-17.beta.-carbothioate. Fluticasone propionate is now used clinically for the treatment of bronchial **asthma** and related disorders.

SUMM [0004] Although tiotropium bromide and fluticasone propionate may be effective therapies, there exists a clinical need for **asthma** therapies having potent and selective action and having an advantageous profile of action.

SUMM . . . which anticholinergic agent and/or an antiinflammatory corticosteroid is indicated Such conditions include diseases associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

SUMM . . . present invention provides such methods for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . aspect, the invention is concerned with the prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . formulations according to the invention may further include other therapeutic agents for example anti-inflammatory agents such as other corticosteroids (e.g. **beclomethasone dipropionate**, mometasone furoate, triamcinolone acetonide or budesonide) or NSAIDs (e.g. sodium cromoglycate, nedocromil sodium. PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists)) or, .beta..sub.2-adrenoreceptor agonists (such as

salbutamol, formoterol, salmeterol, fenoterol or terbutaline and salts thereof), or other anticholinergic agents (such as ipratropium).

DETD . . . be administered by an inhaler such as a Rotahaler, Diskhaler, or Diskus inhaler (each of these being a Trademark of **Glaxo** Group Limited).

CLM What is claimed is:

. . . A method according to claim 6 wherein the clinical condition is a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

L9 ANSWER 10 OF 28 USPATFULL on STN

SUMM . . . 2'-hydroxy-5'-[(RS)-1-hydroxy-2{[(RS)-p-methoxy-.alpha.-methylphenethyl]amino}ethyl]formanilide, particularly its fumarate salt is a well-known adrenoreceptor agonist which is now used clinically in the treatment of bronchial **asthma** and related disorders. Formoterol includes two asymmetric centres and in a particular form exists as the (R,R)-isomer. The (R,R) isomer. . .

SUMM . . . thereof and pharmaceutical formulations thereof. Budesonide is an antiinflammatory corticosteroid, which is now used clinically in the treatment of bronchial **asthma** and related disorders.

SUMM [0005] Although (R,R)-formoterol fumarate and budesonide are effective therapies, there exists a clinical need for **asthma** therapies ~~having potent and selective action and having an advantageous profile of~~ action.

SUMM . . . selective .beta..sub.2-adrenoreceptor agonist and/or an antiinflammatory corticosteroid is indicated. Such conditions include diseases associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

SUMM . . . present invention provides such methods for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . aspect, the invention is concerned with the prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . to the invention may further include other therapeutic agents for example anti-inflammatory agents such as other corticosteroids (e.g. fluticasone propionate, **beclomethasone dipropionate**, mometasone furoate, or triamcinolone acetonide), or NSAIDs (e.g. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists), or other .beta..sub.2-adrenoreceptor agonists (such as **salbutamol**, salmeterol, fenoterol or terbutaline and salts thereof), or anticholinergic agents (such as ipratropium, or tiotropium).

DETD . . . be administered by an inhaler such as a Rotahaler, Diskhaler, or Diskus inhaler (each of these being a Trademark of **Glaxo** Group Limited).

CLM What is claimed is:

4. A pharmaceutical formulation according to claim 3, wherein the other .beta..sub.2-adrenoreceptor agonist is **salbutamol**, salmeterol, fenoterol, terbutaline, or a salt thereof.

. . . A method according to claim 11 wherein the clinical condition is a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

L9 ANSWER 11 OF 28 USPATFULL on STN

SUMM . . . compounds which are .beta..sub.2-adrenoreceptor agonists including 4-hydroxy-.alpha..sup.1-[[[6-(4-phenylbutoxy)hexyl]-amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of bronchial **asthma** and related disorders.

SUMM . . . thereof and pharmaceutical formulations thereof. Rofleponide is an antiinflammatory corticosteroid, which is proposed for use in the treatment of bronchial **asthma** and related disorders.

SUMM [0004] Although salmeterol xinafoate and rofleponide may be effective therapies, there exists a clinical need for **asthma** therapies having potent and selective action and having an advantageous profile of action.

SUMM . . . selective .beta..sub.2-adrenoreceptor agonist and/or an antiinflammatory corticosteroid is indicated. Such conditions include diseases associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

SUMM . . . present invention provides such methods for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . aspect, the invention is concerned with the. prophylaxis or treatment of a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

SUMM . . . to the invention may further include other therapeutic agents for example anti-inflammatory agents such as other corticosteroids (e.g. fluticasone propionate, **beclomethasone dipropionate**, mometasone furoate, triamcinolone acetonide or budesonide) or NSAIDs (e.g. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists), or other .beta..sub.2-adrenoreceptor agonists (such as **salbutamol** , formoterol, fenoterol or terbutaline and salts thereof), or anticholinergic agents (such as ipratropium, or tiotropium).

DETD . . . be administered by an inhaler such as a Rotahaler, Diskhaler, or Diskus inhaler (each of these being a Trademark of **Glaxo** Group Limited).

CLM What is claimed is:

. . . A method according to claim 6 wherein the clinical condition is a disease associated with reversible airways obstruction such as **asthma**, chronic obstructive pulmonary. disease (COPD), respiratory tract infection or upper respiratory tract disease.

L9 ANSWER 12 OF 28 USPATFULL on STN

TI Immunostimulatory nucleic acids for the treatment of **asthma** and allergy

AB The invention involves administration of an immunostimulatory nucleic acid alone or in combination with an **asthma**/allergy medicament for the treatment or prevention of **asthma** and allergy in subjects. The combination of drugs are administered in synergistic amounts or in various dosages or at various. . .

PARN . . . 35 .sctn.119(e), of U.S. Provisional Application No. 60/179,991, filed Feb. 3, 2000, entitled IMMUNOSTIMULATORY NUCLEIC ACIDS FOR THE TREATMENT OF **ASTHMA** AND ALLERGY, the entire contents of which are incorporated herein by reference.

SUMM [0002] **Asthma** is a chronic inflammatory disease effecting 14-15 million persons in the U.S. alone. Symptoms of **asthma** include recurrent episodes of wheezing, breathlessness, and chest tightness, and coughing, resulting from airflow obstruction. Airway inflammation associated with **asthma** can be detected through

observation of a number of physiological changes, such as, denudation of airway epithelium, collagen deposition beneath. . . membrane, edema, mast cell activation, inflammatory cell infiltration, including neutrophils, eosinophils, and lymphocytes. As a result of the airway inflammation, **asthma** patients often experience airway hyper-responsiveness, airflow limitation, respiratory symptoms, and disease chronicity. Airflow limitations include acute bronchoconstriction, airway edema, mucous plug formation, and airway remodeling, features which often lead to bronchial obstruction. In some cases of **asthma**, subbasement membrane fibrosis may occur, leading to persistent abnormalities in lung function.

SUMM [0003] Research over the past several years has revealed that **asthma** likely results from complex interactions among inflammatory cells, mediators, and other cells and tissues resident in the airway. Mast cells, eosinophils, epithelial cells, macrophage, and activated T-cells all play an important role in the inflammatory process associated with **asthma** (Djukanovic et al., Am. Rev. Respir. Dis; 142:434-457; 1990). It is believed that these cells can influence airway function through. . .

SUMM [0004] **Asthma** is a complex disorder which arises at different stages in development and can be classified based on the degree of. . .

SUMM [0005] Medications for the treatment of **asthma** are generally separated into two categories, quick-relief medications and long-term control medications. **Asthma** patients take the long-term control medications on a daily basis to achieve and maintain control of persistent **asthma**. Long-term control medications include anti-inflammatory agents such as corticosteroids, chromolyn sodium and medacromil; long-acting bronchodilators, such as long-acting .beta..sub.2-agonists and. . . each of these drugs and none of the drugs alone or in combination is capable of preventing or completely treating **asthma**.

SUMM . . . The development of an IgE-mediated response to common aeroallergens is also a factor which indicates predisposition towards the development of **asthma**. If an allergen encounters a specific IgE which is bound to an Fc IgE receptor on the surface of a. . . of mediators such as histamine, scrotonin, and lipid mediators. Allergic diseases include but are not limited to rhinitis (hay fever) **asthma**, urticaria and atopic dermatitis.

SUMM [0008] Improved methods and products for the prevention and/or treatment of **asthma** and allergy are provided according to the invention. The invention is based, in some aspects, on the finding that when immunostimulatory nucleic acid molecules are used in conjunction with medicaments for the treatment of **asthma** and allergy, some unexpected and improved results are observed. For instance, the efficacy of the combination of immunostimulatory nucleic acids and **asthma** and allergy medicaments is profoundly improved over the use of each of the medicaments alone. The results are surprising in. . .

SUMM [0009] In some aspects, the invention is a method for preventing or treating **asthma** or allergy by administering a synergistic combination of an immunostimulatory nucleic acid and an **asthma** /allergy medicament, wherein the combination is administered in an effective amount for synergistically reducing the immune or inflammatory response caused by a mediator of **asthma** or allergy. It was surprisingly discovered according to the invention that the combination of the immunostimulatory nucleic acid and the **asthma**/allergy medicament worked synergistically to reduce the immune or inflammatory response initiated when a mediator of **asthma** or allergy is encountered.

SUMM [0010] In other aspects, the invention is a method for altering the dosage of the **asthma**/allergy medicament that is required to treat a subject suffering from **asthma** or allergy. The invention in one aspect is a method for increasing the dose of an **asthma**/allergy medicament without inducing the level of side

effects ordinarily observed with that dose of an **asthma**/allergy medicament. The method is accomplished by administering to a subject suffering from **asthma** or allergy or at risk of developing **asthma** or allergy, an **asthma**/allergy medicament in a dose which would ordinarily induce side effects, administering an immunostimulatory nucleic acid to the subject, wherein administration of the immunostimulatory nucleic acid prevents the side effects associated with the high dose of the **asthma**/allergy medicament. The method provides a basis for administering higher therapeutic doses of an **asthma**/allergy medicament to a subject in order to prevent or reduce the symptoms associated with an asthmatic or an allergic response. . .

SUMM [0011] In another aspect, the invention includes a method for decreasing the dose of an **asthma**/allergy medicament by administering to a subject having **asthma** or allergy or at risk of developing **asthma** or allergy an **asthma**/allergy medicament in a sub-therapeutic dosage and an immunostimulatory nucleic acid, wherein the combination of the sub-therapeutic dose of the **asthma**/allergy medicament and the immunostimulatory nucleic acid produce a therapeutic result in the prevention or treatment of **asthma** or allergy in the subject. The method allows a lower dose of the **asthma**/allergy medicament to be used. This provides several advantages, including lower costs associated with using less drugs and less chances of. . .

SUMM [0012] According to other aspects, the invention involves methods for treating or preventing **asthma** and/or allergy by administering an immunostimulatory nucleic acid and an **asthma**/allergy medicament in different dosing schedules. In one aspect, the invention is a method for preventing or treating **asthma** or allergy by administering to a subject an effective amount of an immunostimulatory nucleic acid in an effective amount for producing the immune response and subsequently administering to the subject an **asthma**/allergy medicament. In other aspects, the invention is a method for preventing or treating **asthma** or allergy by administering to a subject an allergy/**asthma** medicament in an effective amount for providing some symptomatic relief and subsequently administering an immunostimulatory nucleic acid to the subject.. . .

SUMM [0013] In another aspect of the invention is a method for treating **asthma** or allergy by administering to a subject having **asthma** or allergy or at risk of developing **asthma** or allergy an immunostimulatory nucleic acid and an **asthma**/allergy medicament, wherein the immunostimulatory nucleic acid is administered systemically and the **asthma**/allergy medicament is administered locally. In yet another aspect, the immunostimulatory nucleic acid is administered locally and the **asthma**/allergy medicament is administered systemically.

SUMM [0014] According to yet another aspect of the invention, a method for treating or preventing **asthma**/allergy is provided. The method is accomplished by administering to a subject having **asthma** or allergy or at risk of developing **asthma** or allergy, an immunostimulatory nucleic acid and an **asthma**/allergy medicament on a routine schedule. In some embodiments, the routine schedule is a daily, weekly, monthly, or quarterly administration of the medicaments. In other embodiments, the immunostimulatory nucleic acid and/or the **asthma**/allergy medicament is administered in two or more doses.

SUMM . . . more doses. Alternatively, it can be administered on a non-regular basis e.g. whenever symptoms being. In yet other embodiments, the **asthma**/allergy medicament is a quick relief **asthma**/allergy medicament and in other embodiments it is a long-lasting **asthma**/allergy medicament.

SUMM [0016] According to yet another aspect of the invention, methods for treating or preventing **asthma** or allergy using specific immunostimulatory nucleic acid molecules are provided. The method in one

aspect involves a method for preventing or treating **asthma** or allergy by administering to a subject suffering from **asthma** or allergy or at risk of developing **asthma** or allergy, an immunostimulatory nucleic acid having a sequence selected from the group consisting of SEQ ID NO:1 through to SEQ ID NO:1093 and administering to the subject an **asthma**/allergy medicament.

SUMM [0017] In yet another aspect of the invention, a method for preventing or treating **asthma** or allergy utilizing different routes of administration is provided. In one aspect, the method involves the step of administering to a subject having **asthma** or allergy or at risk of developing **asthma** or allergy, an immunostimulatory nucleic acid, wherein the immunostimulatory is administered systemically and wherein the **asthma**/allergy medicament is administered locally. In a related embodiment, the immunostimulatory nucleic acid molecule may be administered locally and the **asthma**/allergy medicament is administered systemically. In still other embodiments, the immunostimulatory nucleic acid and the **asthma**/allergy medicament are administered by the same route (i.e., both delivered locally or both delivered systemically), and optionally at the same. . .

SUMM [0018] The invention according to another aspect is a method of preventing or treating **asthma** or allergy by administering a poly-G nucleic acid, in an effective amount for treating or preventing **asthma** or allergy. In some embodiments the poly-G nucleic acid is administered alone and in other embodiments the poly-G nucleic acid is administered in conjunction with an **asthma**/allergy medicament. The poly-G nucleic acid in preferred embodiments comprises one of the following formulas: 5' X.sub.1X.sub.2GGGX.sub.3X.sub.43', wherein X.sub.1, X.sub.2, X.sub.3,. . .

SUMM [0021] The invention provides, in yet another aspect, a method for treating or preventing **asthma** or allergy in a hypo-responsive subject. The method involves administering to a hypo-responsive subject having **asthma** or allergy or at risk of developing **asthma** or allergy an immunostimulatory nucleic acid. In one embodiment, the method further comprises administering to the hypo-responsive subject an **asthma**/allergy medicament. If the **asthma**/allergy medicament is not administered to the hypo-responsive subject, then the immunostimulatory nucleic acid is administered in an amount to treat or prevent the **asthma** or allergy. If the **asthma**/allergy medicament is administered to the hypo-responsive subject, then the immunostimulatory nucleic acid and the **asthma**/allergy medicament are administered in an effective amount to treat or prevent the **asthma** or allergy. In this latter instance, the amount of the immunostimulatory nucleic acid and the amount of the **asthma**/allergy medicament may be insufficient (i.e., ineffective) in treating or preventing the **asthma** or allergy if administered alone. In other words, in some embodiments, the immunostimulatory nucleic acid may be administered to the hypo-responsive subject in a sub-therapeutic amount. Similarly, the **asthma**/allergy medicament may also be administered in a sub-therapeutic amount. However, the combination of the immunostimulatory nucleic acid and the **asthma**/allergy medicament allows for lower doses of one or both in order to treat or prevent the **asthma** or allergy. The immunostimulatory nucleic acid may be administered concurrently with the **asthma**/allergy medicament, but need not be.

SUMM [0022] The hypo-responsive subject may be one who is hypo-responsive to an **asthma**/allergy medicament. In one embodiment, the hypo-responsive subject is selected from the group consisting of a subject who is refractory to an **asthma**/allergy medicament, a subject who is a non-responder to an **asthma**/allergy medicament, an elderly subject and a neonatal subject.

SUMM [0023] According to yet another aspect of the invention, a method is provided for preventing **asthma** or allergy in a subject at risk

of developing **asthma** or allergy which involves administering to a subject at risk of developing **asthma** or allergy an effective amount of an immunostimulatory nucleic acid substantially prior to an asthmatic or an allergic event.

SUMM [0025] In one embodiment, the asthmatic or allergic event is selected from the group consisting of an **asthma** attack, seasonal allergic rhinitis, and perennial allergic rhinitis.

SUMM [0027] In a further aspect, the invention provides another method for decreasing a dose of an **asthma**/allergy medicament. The method involves administering to a subject at risk of developing **asthma** or allergy, substantially prior to an asthmatic or allergic event, an immunostimulatory nucleic acid in an amount to decrease an effective amount of an **asthma**/allergy medicament subsequently administered to the subject in order to treat the **asthma** or allergy.

SUMM [0029] In one embodiment, the asthmatic or allergic event is selected from the group consisting of an **asthma** attack, seasonal allergic rhinitis, and perennial allergic rhinitis.

SUMM [0031] The method may further comprise administering to the subject the **asthma**/allergy medicament subsequent to the administration of the immunostimulatory nucleic acid. In one embodiment, the **asthma**/allergy medicament is administered immediately prior to, concurrently with, or following the asthmatic or allergic event. The method may further comprise. . . with or following the asthmatic or allergic event. In one embodiment, the immunostimulatory nucleic acid is administered concurrently with the **asthma**/allergy medicament. In one embodiment, the **asthma**/allergy medicament is administered in a sub-therapeutic dose.

SUMM [0033] In these and other aspects of the invention, the **asthma** /allergy medicaments have a number of attributes. In some embodiments, the **asthma**/allergy medicament is an **asthma** medicament, while in still other embodiments, the **asthma** /allergy medicament is an allergy medicament.

SUMM [0034] In some embodiments, the **asthma**/allergy medicament is selected from the group consisting of a steroid and an immunomodulator. In certain embodiments, the steroid may be. . .

SUMM [0035] In some embodiments, the **asthma**/allergy medicament is a medicament selected from the group consisting of a PDE-4 inhibitor, a bronchodilator/beta-2 agonist, a K.sup.+ channel opener,. . . protein, and a protease inhibitor. In certain embodiments, the bronchodilator/beta-2 agonist may be selected from the group consisting of salmeterol, **salbutamol**, terbutaline, D2522/formoterol, fenoterol and orciprenaline.

SUMM [0036] In some embodiments, the **asthma**/allergy medicament is a medicament selected from the group consisting of an anti-histamine and a prostaglandin inducer. In certain embodiments, the. . .

SUMM [0037] In still other embodiments, the **asthma**/allergy medicament is a prostaglandin inhibitor in the form of a cyclooxygenase-2 (COX-2) inhibitor. The COX-2 inhibitor may be selected from. . .

SUMM . . . kit in one aspect includes a sustained-release vehicle containing an immunostimulatory nucleic acid and at least one container housing an **asthma**/allergy medicament, and instructions for timing of administration of the immunostimulatory nucleic acid and the **asthma**/allergy medicament. In another aspect, the kit includes containers for multiple administrations of immunostimulatory nucleic acid and/or multiple administrations of immunostimulatory nucleic acid and at least one container housing an **asthma**/allergy medicament.

SUMM . . . A composition is provided according to another aspect of the invention. The composition includes an immunostimulatory nucleic acid and an **asthma**/allergy medicament, formulated in a pharmaceutically-acceptable carrier and in an effective amount for preventing or treating an immune response associated with exposure to a

mediator of **asthma** or allergy.

SUMM [0043] The **asthma**/allergy medicament may be any of the **asthma** medicaments or allergy medicaments described above which are useful in other aspects of the invention.

DETD [0045] The invention relates to methods and products for the treatment of **asthma**/allergy using a combination of immunostimulatory nucleic acids and **asthma**/allergy medicaments. The compositions can be administered in higher doses without as many side effects as are ordinarily achieved at those. . . in different temporal relationships to one another. The various combinations have many advantages over the prior art methods of treating **asthma** and allergy.

DETD [0046] One method for treating or preventing **asthma** or allergy includes the step of administering a synergistic combination of an immunostimulatory nucleic acid and an **asthma**/allergy medicament in an effective amount to treat or prevent the **asthma** or allergy.

DETD [0048] The immunostimulatory nucleic acids when combined with the **asthma**/allergy medicaments have many advantages over each composition alone for the treatment of **asthma** and allergy. The immunostimulatory nucleic acid functions in some aspects by simultaneously suppressing Th2-type immune responses (IL-4, IgE production, histamine. . .

DETD [0049] The immunostimulatory nucleic acids eliminate/reduce bronchial hyperreactivity, bronchoconstriction, bronchial obstruction, airway ~~inflammation and atopy (which improves **asthma** control,~~ normalizes lung function, prevents irreversible airway injury); and may also inhibit acute response to exercise, cold dry air, and. . .

DETD [0050] Immunostimulatory nucleic acids stimulate the immune system to prevent or treat allergy and/or **asthma**. The strong yet balanced, cellular and humoral immune responses that result from the nucleic acid's stimulation reflect the body's own. . .

DETD [0066] In some aspects of the invention the poly-G containing nucleic acids are administered alone for the treatment of **asthma** and allergy. It was previously suggested in the prior art that poly-G rich oligonucleotides inhibit the production of IFN-.delta. by. . . the invention that when poly-G nucleic acids are administered in vivo, they are useful for treating or preventing allergy or **asthma**. Thus, in this aspect of the invention, poly-G nucleic acids are administered alone or optionally with other **asthma**/allergy medicaments for the treatment of allergy and/or **asthma**.

DETD [0086] The immunostimulatory nucleic acids are useful for treating or preventing allergy or **asthma** in a subject. A "subject" shall mean a human or vertebrate mammal including but not limited to a dog, cat,. . .

DETD . . . aspects of the invention as a prophylactic for the treatment of a subject at risk of developing an allergy or **asthma** where the exposure of the subject to an allergen or predisposition to **asthma** is known or suspected. A "subject at risk" of developing allergy or **asthma** as used herein is a subject who has any risk of exposure to an allergen or a risk of developing **asthma**, i.e. someone who has suffered from an asthmatic attack previously or has a predisposition to asthmatic attacks. For instance, a. . . then that subject is at risk of exposure to the antigen. A subject at risk of developing an allergy or **asthma** includes those subjects that have been identified as having an allergy or **asthma** but that don't have the active disease during the treatment of the invention as well as subjects that are considered. . .

DETD [0088] In addition to the use of the immunostimulatory nucleic acid and the **asthma**/allergy medicament for prophylactic treatment, the invention also encompasses the use of the combination of drugs for the treatment of a subject having an allergy or **asthma**. A "subject having an allergy" is a subject that has an allergic reaction in response to an allergen. An "allergy". . .

DETD . . . diseases in humans include but are not limited to eczema,

allergic rhinitis or coryza, hay fever, conjunctivitis, bronchial or allergic **asthma**, urticaria (hives) and food allergies; atopic dermatitis; anaphylaxis; drug allergy; angioedema; and allergic conjunctivitis. Allergic diseases in dogs include but are not limited to seasonal dermatitis; perennial dermatitis; rhinitis: conjunctivitis; allergic **asthma**; and drug reactions. Allergic diseases in cats include but are not limited to dermatitis and respiratory disorders; and food allergens.. . . to respiratory disorders such as "heaves" and dermatitis. Allergic diseases in non-human primates include but are not limited to allergic **asthma** and allergic dermatitis.

DETD . . . inflammatory disorders. In contrast Th2-type responses are responsible for triggering allergic atopic disorders (against common environmental allergens) such as allergic **asthma** (Walker et al, 1992, Am Rev Resp Dis 148: 109-115) and atopic dermatitis (van der Heijden et al, 1991, J. . .

DETD . . . the immune response in a subject from a Th2 (which is associated with production of IgE antibodies and allergy and **asthma**) to a Th1 response (which is protective against allergic and asthmatic reactions), an effective dose for inducing an immune response of a immunostimulatory nucleic acid can be administered to a subject to treat or prevent an allergy or **asthma**.

DETD . . . production of Th2 cytokines. Thus, the immunostimulatory nucleic acid has significant therapeutic utility in the treatment of allergic conditions and **asthma**.

~~DETD . . . acid anhydrides (such as trimellitic anhydride) and the~~ isocyanates (such as toluene diisocyanate)); Occupational Allergens such as flour (ie. Baker's **asthma**), castor bean, coffee bean, and industrial chemicals described above; flea allergens; and human proteins in non-human animals.

DETD [0102] A "subject having **asthma**" is a subject that has a disorder of the respiratory system characterized by inflammation, narrowing of the airways and increased reactivity of the airways to inhaled agents. **Asthma** is frequently, although not exclusively associated with atopic or allergic symptoms. An "initiator" as used herein refers to a composition or environmental condition which triggers **asthma**. Initiators include, but are not limited to, allergens, cold temperatures, exercise, viral infections, SO.sub.2.

DETD [0103] In another aspect the invention provides methods for treating or preventing **asthma** or allergy in a hypo-responsive subject. As used herein, a hypo-responsive subject is one who has previously failed to respond to a treatment directed at treating or preventing **asthma** or allergy or one who is at risk of not responding to such a treatment. The treatment directed at treating or preventing **asthma** or allergy may be an **asthma**/allergy medicament, in which case the hypo-responsive subject is one who is hypo-responsive to an **asthma**/allergy medicament.

DETD [0104] Other subjects who are hypo-responsive include those who are refractory to an **asthma**/allergy medicament. As used herein, the term "refractory" means resistant or failure to yield to treatment. Such subjects may be those who never responded to an **asthma** /allergy medicament (i.e., subjects who are non-responders), or alternatively, they may be those who at one time responded to an **asthma**/allergy medicament, but have since that time have become refractory to the medicament. In some embodiments, the subject is one who. . .

DETD . . . elderly subjects, regardless of whether they have or have not previously responded to a treatment directed at treating or preventing **asthma** or allergy. Elderly subjects, even those who have previously responded to such treatment, are considered to be at risk of. . . Similarly, neonatal subjects are also considered to be at risk of not responding to treatment directed at treating or preventing **asthma** or allergy.

DETD [0106] In some embodiments, an immunostimulatory nucleic acid is administered to the hypo-responsive subject without the further

administration of an **asthma**/allergy medicament. In yet other embodiments, an **asthma**/allergy medicament is administered to the hypo-responsive subject, in which case it may be administered substantially simultaneously (i.e., concurrently) with, or. . .

DETD [0107] An "**asthma**/allergy medicament" as used herein is a composition of matter which reduces the symptoms, inhibits the asthmatic or allergic reaction, or prevents the development of an allergic or asthmatic reaction. Various types of medicaments for the treatment of **asthma** and allergy are described in the Guidelines For The Diagnosis and Management of **Asthma**, Expert Panel Report 2, NIH Publication No. 97/4051, Jul. 19, 1997, the entire contents of which are incorporated herein by. . .

DETD [0108] In most embodiments the **asthma**/allergy medicament is useful to some degree for treating both **asthma** and allergy. Some **asthma**/allergy medicaments are preferably used in combination with the immunostimulatory nucleic acids to treat **asthma**. These are referred to as **asthma** medicaments. **Asthma** medicaments include, but are not limited, PDE-4 inhibitors, bronchodilator/beta-2 agonists, K.sup.+ channel openers, VLA-4 antagonists, neurokin antagonists, TXA2 synthesis inhibitors,. . .

DETD . . . a class of compounds which cause bronchodilation or smooth muscle relaxation. Bronchodilator/beta-2 agonists include, but are not limited to, salmeterol, **salbutamol**, albuterol, terbutaline, D2522/formoterol, fenoterol, bitolterol, pirbuerol methylxanthines and orciprenaline. Long-acting P2 agonists and bronchodilators are compounds which are used for. . .

DETD . . . of acute asthmatic systems. Previously, short-acting .beta..sub.2 agonists had been prescribed on a regularly-scheduled basis in order to improve overall **asthma** symptoms. Later reports, however, suggested that regular use of this class of drugs produced significant diminution in **asthma** control and pulmonary function (Sears, et al. Lancet; 336:1391-6, 1990). Other studies showed that regular use of some types of. . .

DETD [0111] Other **asthma**/allergy medicaments are preferably used in combination with the immunostimulatory nucleic acids to treat allergy. These are referred to as allergy. . .

DETD [0112] The **asthma**/allergy medicaments useful in combination with the immunostimulatory nucleic acids also include steroids and immunomodulators.

DETD . . . and triamcinoone acetonide. Although dexamethasone is a corticosteroid having anti-inflammatory action, it is not regularly used for the treatment of **asthma**/allergy in an inhaled form because it is highly absorbed, it has long-term suppressive side effects at an effective dose. Dexamethasone, however, can be used according to the invention for the treating of **asthma**/allergy because when administered in combination with immunostimulatory nucleic acids it can be administered at a low dose to reduce the. . .

DETD . . . necrosis of femur. These compounds are useful for short-term (3-10 days) prevention of the inflammatory reaction in inadequately controlled persistent **asthma**. They also function in a long-term prevention of symptoms in severe persistent **asthma** to suppress and control and actually reverse inflammation. The side effects associated with systemic corticosteroids are even greater than those. . . recommended that these types of compounds be used at their lowest effective dose (guidelines for the diagnosis and management of **asthma**; expert panel report to; NIH Publication No. 97-4051; July 1997). The inhaled corticosteroids are believed to function by blocking late. . .

DETD [0118] Leukotriene modifiers are often used for long-term control and prevention of symptoms in mild persistent **asthma**. Leukotriene modifiers function as leukotriene receptor antagonists by selectively competing for LTD-4 and LTE-4 receptors. These compounds include, but are. . . of airway smooth muscle and increase vascular permeability,

mucous secretions and activate inflammatory cells in the airways of patients with **asthma**.

DETD [0122] These types of **asthma**/allergy medicaments are sometimes classified as long-term control medications or quick-relief medications. Long-term control medications include compounds such as corticosteroids (also. . .

DETD [0123] Chromolyn sodium and medocromil are used as long-term control medications for preventing primarily **asthma** symptoms arising from exercise or allergic symptoms arising from allergens. These compounds are believed to block early and late reactions. . .

DETD [0125] In addition to standard **asthma**/allergy medicaments other methods for treating **asthma**/allergy have been used either alone or in combination with established medicaments. One preferred, but frequently impossible, method of relieving allergies. . .

DETD . . . are associated with the risk of side effects such as anaphylactic shock. The use of an immunostimulatory nucleic acid and **asthma**/allergy medicament in combination with an allergen avoids many of the side effects etc.

DETD [0128] Commonly used allergy and **asthma** drugs which are currently in development or on the market are shown in Tables 1 and 2 respectively.

TABLE 1

Allergy. . .	Claritin D (loratidine)	Anti-histamine
Plough	Vancenase (beclomethasone)	Steroid
UCB	Reactine (cetirizine) (US)	Anti-histamine
	Zyrtec (cetirizine) (ex US)	
	Longifene (buclizine)	Anti-histamine
	UCB 28754 (ceterizine alalogue)	Anti-histamine
Glaxo	Beconase (beclomethasone	Steroid
	Flonase (fluticasone)	Steroid
Aventis	Allegra (fexofenadine)	Anti-histamine
	Seldane (terfenadine)	Anti-histamine
Pfizer	Reactine (cetirizine) (US)	Anti-histamine
	Zyrtec/Reactine (cetirizine) (ex US) (both. . . pollen allergy)	Other
Asta Medica	Azelastine-MDPI (azelastine)	Anti-histamine
BASF	HSR 609	Anti-histamine
SR Pharma	SRL 172	Immunomodulation
Peptide Therapeutics	Allergy vaccine (allergy (hayfever, anaphylaxis, atopic **asthma**) Downregulates specific IgE	
	Tolerizing peptide vaccine (rye grass peptide (T cell epitope))	Immuno-suppressant
Coley	CpG DNA	Immunomodulation

Pharmaceutical
Group
Genetech Anti-IgE
Down-regulaotr of
. . .
DETD [0129]
TABLE 2

Asthma Drugs in Development or on the Market

MARKETER	BRAND NAME (GENERIC NAME)	MECHANISM
Glaxo	Serevent (salmeterol)	
	Bronchodilator/beta-2 agonist	
	Flovent (fluticasone)	Steroid
	Flixotide (fluticasone)	
	Becotide (betamethasone)	Steroid
	Ventolin (**salbutamol**)	
	Bronchodilator/beta-2 agonist	
	Seretide (salmeterol + fluticasone)	Beta
	agonist + steroid	
	GW215864	Steroid,
	hydolysable	
	GW250495	Steroid,
	hydolysable	
	GW328267	Adenosine
	A2 agonist	
AstraZeneca. . .	(Astra)	
	Pulmicort (budesonide) (Astra)	Steriod
	Bricanyl Turbuhaler (terbutaline) (Astra)	
	Bronchodilator/beta-2 agonist	
	Accolate (zafirlukast) (Zeneca)	
	Leukotriene antagonist Slo-	
		Phyllin
	(theophylline)	
	Inspiryl (**salbutamol**) (Astra)	
	Bronchodilator/beta-2 agonist	
	Oxis Turbuhaler (D2522/formoterol)	
	Bronchodilator/beta-2 agonist	
	Symbicort (pulmicort-oxis combination)	Steroid
	Roflepanide (Astra)	Steroid
	Bronica (seratrodast)	TXA2
	synthesis inhibitor	
. . .	Spiropent (clenbuterol)	
	Bronchodilator/beta-2 agonist	
	Inhacort (flunisolide)	Steroid
	B1679/tiotropium bromide	
	RPR 106541	Steroid
	BIIX 1	Potassium
	channel	
	BIIL284 LTB-4	
	antagonist	
Schering-	Proventil (**salbutamol**)	
	Bronchodilator/beta-2 agonist	
Plough		
	Vanceril (becbomethasone)	Steroid
	Mometasone furoate	Steroid
	Theo-Dur (theophylline (w/Astra)	
	Uni-Dur (theophylline)	
	Asmanex (mometasone)	Steroid
	CDP 835 (lic from. . . (pranlukast)	
	Leukotriene antagonist	
	Vega (ozagrel)	TXA2
	synthesis inhibitor	

Fujisawa	Intal (chromoglycate)	
	Anti-inflammatory	
	FK 888	Neurokin
	antagonist	
Forest Labs	Aerobid (flunisolide)	Steroid
IVAX	Ventolin (**salbutamol**)	
	Bronchodilator/beta-2 agonist	
	Becotide (beclomethasone Easi-Breathe)	Steroid
	Serevent (salmeterol)	
	Bronchodilator/beta-2 agonist	
	Flixotide (fluticasone)	Steroid
	Budesonide Dry Powder Inhaler	Steroid
	Salbutamol Dry Powder Inhaler	
	Bronchodilator/beta-2 agonist	
Alza	Volmax (**salbutamol**)	
	Bronchodilator/beta-2 agonist	
Altana	Euphyllin (theophylline)	
	Xanthanine	
	Ciclesonide	
	Arachidonic acid antagonist	
	BY 217	PDE 4
	inhibitor	
	BY 9010N (ciclesonide)	Steroid
	(nasal)	
~~Tanabe~~	~~Flucort. . . (zileuton) (4X/day dosing, not competitive w/~~	
	5 lipoxygenase inhibitor	
	Singulair or Accolate, no further interest in this area)	
Asta Medica	Aerobec (**beclomethasone dipropionate**)	
	(w/3M)	
	Allergodil (azelastine)	
	Allergospasmin (sodium cromoglycate reproterol)	
	Bronchospasmin (reproterol)	
	Salbulair (**salbutamol** sulphate) (w/3M)	
	TnNasal (triamcinolone)	Steroid
	Formoterol-MDPI	Beta 2
	adrenoceptor agonist	
	Budesonide-MDPI	
UCB	Atenos/Respecal (tulobuerol)	
	Bronchodilator/beta-2 agonist	
Recordati	Theodur (theophylline)	Xanthine
Medeva	Clickhalers Asmasal, Asmabec (**salbutamol**	
	Steroid	
	beclomethasone diproprionate, dry inhaler)	
Eisai	E6123	PAF
	receptor antagonist	
Sankyo	Zaditen (ketotifen)	
	Anti-inflammatory	
	CS 615	
	Leukotriene antagonist	
Shionogi	Anboxan/S 1452 (domitroban)	
	Thromboxin. . . to Schering-	IL-5 antagonist Mab
Chiroscience	Plough)	
	D 4418 (w/ Schering-Plough)	PDE 4
	inhibitor	
	CDP 840 (Celltech)	PDE 4
	inhibitor	
AHP	Pda-641 (**asthma** steroid replacement)	
Peptide	RAPID Technology Platform	Protease
	inhibitors	
Therapeutics		
Coley	CpG DNA	
	Immunomodulation	
Pharmaceutical		
Group		

DETD . . . cases the subject is exposed to an allergen in addition to being treated with the immunostimulatory nucleic acid and the **asthma**/allergy medicament. In this case the subject is said to be exposed to the allergen. As used herein, the term "exposed. . . or subcutaneous administration. The allergen can be administered systemically or locally. Methods for administering the allergen and the immunostimulatory nucleic acid/**asthma**/allergy medicament are described in more detail below. A subject is passively exposed to an allergen if an allergen becomes available. . .

DETD . . . passively exposed to an allergen can be particularly dependent on timing of administration of the immunostimulatory nucleic acid and the **asthma**/allergy medicament. For instance, in a subject at risk of developing an allergic or asthmatic response, the subject may be administered the immunostimulatory nucleic acid and the **asthma** /allergy medicament on a regular basis when that risk is greatest, i.e., during pollen allergy season. Additionally the immunostimulatory nucleic acid and the **asthma**/allergy medicament may be administered to travelers before they travel to a destination where they are at risk of exposure to. . .

DETD . . . or initiator as well as a treatment after the allergic or asthmatic disorder has begun in order to fight the allergy/ **asthma**, e.g., reduce or eliminate it altogether or prevent it from becoming worse.

DETD [0134] The allergen and/or polypeptide **asthma**/allergy medicament may be in the form of a polypeptide when administered to the subject or it may be encoded by. . .

DETD [0135] The nucleic acid encoding the allergen or **asthma** /allergy medicament is operatively linked to a gene expression sequence which directs the expression of the protein within a eukaryotic cell.. . .

DETD . . . In some embodiments, one plasmid vector could include both the immunostimulatory nucleic acid and a nucleic acid encoding a protein **asthma**/allergy medicament and/or an allergen. In other embodiments, separate plasmids could be used. In yet other embodiments, no plasmids could be. . .

DETD . . . into two classes: biological vectors and chemical/physical vectors. Biological vectors and chemical/physical vectors are useful for delivery/uptake of nucleic acids, **asthma**/allergy medicaments, and/or allergens to/by a target cell.

DETD [0146] In addition to the biological vectors, chemical/physical vectors may be used to deliver a nucleic acid, **asthma**/allergy medicament, and/or allergen to a target cell and facilitate uptake thereby. As used herein, a "chemical/physical vector" refers to a natural or synthetic molecule, other than those derived from bacteriological or viral sources, capable of delivering the nucleic acid, **asthma**/allergy medicament, and/or allergen to a cell.

DETD . . . The polymeric matrix preferably is in the form of a microparticle such as a microsphere (wherein the a nucleic acid, **asthma**/allergy medicament, and/or allergen is dispersed throughout a solid polymeric matrix) or a microcapsule (wherein the a nucleic acid, **asthma**/allergy medicament, and/or allergen is stored in the core of a polymeric shell). Other forms of the polymeric matrix for containing the a nucleic acid, **asthma**/allergy medicament, and/or allergen include films, coatings, gels, implants, and stents. The size and composition of the polymeric matrix device is. . . into the nasal and/or pulmonary areas. Preferably when an aerosol route is used the polymeric matrix and the nucleic acid, **asthma** /allergy medicament, and/or allergen are encompassed in a surfactant vehicle. The polymeric matrix composition can be selected to have both favorable. . .

DETD [0154] Both non-biodegradable and biodegradable polymeric matrices can be used to deliver the nucleic acid, **asthma**/allergy medicament, and/or allergen to the subject. Biodegradable matrices are preferred. Such polymers may be natural or synthetic polymers. The

polymer. . .

DETD [0157] Other exemplary compositions that can be used to facilitate uptake by a target cell of the nucleic acid, **asthma**/allergy medicament, and/or allergen include calcium phosphate and other chemical mediators of intracellular transport, microinjection compositions, electroporation and homologous recombination compositions. . .

DETD [0158] The immunostimulatory nucleic acid and/or the **asthma** /allergy medicament the antigen and/or other therapeutics may be administered alone (e.g. in saline or buffer) or using any delivery vectors. . .

DETD [0159] The immunostimulatory nucleic acid and **asthma**/allergy medicament can be combined with other therapeutic agents such as adjuvants to enhance immune responses even further. The immunostimulatory nucleic acid, **asthma**/allergy medicament and other therapeutic agent may be administered simultaneously or sequentially. When the other therapeutic agents are administered simultaneously they. . . the same time. The other therapeutic agents are administered sequentially with one another and with the immunostimulatory nucleic acid and **asthma**/allergy medicament, when the administration of the other therapeutic agents and the immunostimulatory nucleic acid and **asthma**/allergy medicament is temporally separated. The separation in time between the administration of these compounds may be a matter of minutes. . .

DETD . . . al., 1997) or B-7 co-stimulatory molecules (Iwasaki et al., 1997; Tsuji et al., 1997) with the immunostimulatory nucleic acids and **asthma**/allergy medicaments. The cytokines can be administered directly with immunostimulatory nucleic acids or may be administered in the form of a. . .

DETD [0166] The term "effective amount" of an immunostimulatory nucleic acid and an **asthma**/allergy medicament refers to the amount necessary or sufficient to realize a desired biologic effect. For example, an effective amount of an immunostimulatory nucleic acid and an **asthma**/allergy medicament for treating or preventing **asthma** or preventing is that amount necessary to prevent the development of IgE in response to an allergen or initiator upon. . .

DETD . . . application can vary depending on such factors as the disease or condition being treated, the particular immunostimulatory nucleic acid or **asthma**/allergy medicament being administered (e.g. the type of nucleic acid, i.e. a CpG nucleic acid, the number of unmethylated CpG motifs. . . One of ordinary skill in the art can empirically determine the effective amount of a particular immunostimulatory nucleic acid and/or **asthma**/allergy medicament and/or other therapeutic agent without necessitating undue experimentation.

DETD [0168] Depending upon the aspect of the invention, the immunostimulatory nucleic acid and **asthma**/allergy medicament may be administered in a synergistic amount effective to treat or prevent **asthma** or allergy. A synergistic amount is that amount which produces a physiological response that is greater than the sum of the individual effects of either the immunostimulatory nucleic acid or the **asthma**/allergy medicament alone. For instance, in some embodiments of the invention, the physiological effect is a reduction in IgE levels. A. . . in IgE that is greater than the sum of the IgE reduced by either the immunostimulatory nucleic acid or the **asthma**/allergy medicament alone. In other embodiments, the physiological result is a shift from Th2 cytokines, such as IL-4 and IL-5, to. . . Th1 cytokine that is greater than the sum of the shift produced by either the immunostimulatory nucleic acid or the **asthma**/allergy medicament alone. In other embodiments the physiological result is a decrease in eosinophilia, hyperreactivity, or lung function.

DETD . . . are known to be useful for preventing bacterial and viral infections. Bacterial and viral infections exacerbate and/or induce allergy and/or **asthma**. In this aspect of the invention, the

immunostimulatory nucleic acid is administered to the subject in an amount effective to prevent bacterial and viral infection and the **asthma**/allergy medicament is administered to the subject when symptoms of allergy or **asthma** appear. Thus, the immunostimulatory nucleic acid is administered to the subject and then the **asthma**/allergy medicament is subsequently administered to the subject or they are administered together at the same time. This method is particularly. . .

DETD . . . of the hay-fever season), the subjects may be administered an immunostimulatory nucleic acid in an effective amount for preventing the **asthma** or allergy. In related embodiments of this method, an **asthma**/allergy medicament is also administered to the subject. In these latter instances, the amount of the immunostimulatory nucleic acid administered may be that amount necessary to reduce the effective dose of the **asthma**/allergy medicament which is required to treat or prevent the **asthma** or allergy.

DETD [0171] Thus, in these embodiments, the immunostimulatory nucleic acid potentiates the effect of the **asthma**/allergy medicament. The ability to potentiate the effect of an **asthma**/allergy medicament is useful since it allows for a reduction in the administered dose of an **asthma**/allergy medicament with the same or better therapeutic result. As an example, if the dose of the medicament is lowered, then. . . as, for example, drowsiness, nervousness, dizziness or, in some instances, sleeplessness. Similarly, the administration of a lowered dose of the **asthma**/allergy medicament may make the medicament more compatible with the administration of other medicaments such as those which are currently not simultaneously prescribed or administered with **asthma** or allergy medicaments. In some instances, these include certain medicaments which are prescribed for depression, psychiatric or emotional conditions or Parkinson's disease and which contain monoamine oxidase inhibitor (MAOI). Similarly, the ability to potentiate the effect of the **asthma**/allergy medicament, thereby leading to a decreased effective dose, is useful for treating a wide range of subjects who have previously. . . who are nursing (i.e., breast-feeding). Thus, the invention provides a method for administering to a subject a dose of an **asthma**/allergy medicament which if administered alone, or if administered without previous administration of an immunostimulatory nucleic acid to the same subject,. . .

DETD [0173] In some instances, a sub-therapeutic dosage of the immunostimulatory nucleic acid and the **asthma**/allergy medicament are used. It has been discovered according to the invention, that when the two classes of drugs are used. . . that dosage which would produce a therapeutic result in the subject, if administered alone. Thus, the sub-therapeutic dose of an **asthma**/allergy medicament is one which would not produce the desired therapeutic result in the subject. Therapeutic doses of **asthma**/allergy medicaments are well known in the field of medicine for the treatment of **asthma** and allergy. These dosages have been extensively described in references such as Remington's Pharmaceutical Sciences, 18th ed., 1990; as well as many other medical references relied upon by the medical profession as guidance for the treatment of **asthma** and allergy. Therapeutic dosages of immunostimulatory nucleic acids, have also been described in the art and methods for identifying therapeutic. . .

DETD [0174] In other aspects, the method of the invention involves administering a high dose of an **asthma**/allergy medicament to a subject, without inducing side effects. Ordinarily, when an **asthma**/allergy medicament is administered in a high dose, a variety of side effects can occur. (Discussed in more detail above, as well as in the medical literature). As a result of these side effects, the **asthma**/allergy medicament is not administered in such high doses, no matter what therapeutic benefits are derived. It was discovered, according to the invention, that such high doses of

asthma/allergy medicaments which ordinarily induce side effects can be administered without inducing the side effects as long as the subject also receives an immunostimulatory nucleic acid. The type and extent of the side effects ordinarily induced by the **asthma** /allergy medicament will depend on the particular **asthma** /allergy medicament used.

DETD [0175] In other embodiments of the invention, the immunostimulatory nucleic acid is administered on a routine schedule. The **asthma** /allergy medicament may also be administered on a routine schedule, but alternatively, may be administered as symptoms arise. A "routine schedule". . .

DETD . . . prevent an asthmatic or allergic event. The asthmatic or allergic event may be, but need not be limited to, an **asthma** attack, seasonal allergic rhinitis (e.g., hay-fever, pollen, ragweed hypersensitivity) or perennial allergic rhinitis (e.g., hypersensitivity to allergens such as those. . .

DETD [0177] Similarly, the **asthma**/allergy medicament may be administered immediately prior to the asthmatic or allergic event (e.g., within 48 hours, within 24 hours, within. . . asthmatic or allergic event (e.g., during the time the subject is in contact with the allergen or is experiencing the **asthma** or allergy symptoms) or following the asthmatic or allergic event.

DETD [0178] In some embodiments, the immunostimulatory nucleic acid and the **asthma**/allergy medicament are both administered to a subject. ~~The timing of administration of both may vary. In some embodiments, it~~ is preferred that the **asthma**/allergy medicament be administered subsequent to the administration of the immunostimulatory nucleic acid. In some embodiments, the immunostimulatory nucleic acid is administered to the subject prior to as well as either substantially simultaneously with or following the administration of the **asthma**/allergy medicament. The administration of the immunostimulatory nucleic acid and the **asthma**/allergy medicament may also be mutually exclusive of each other so that at any given time during the treatment period, only. . .

DETD [0179] In some embodiments, the immunostimulatory nucleic acid is administered on a weekly or biweekly basis and the **asthma** /allergy medicament is administered more frequently (e.g., on a daily basis). However, if the dose of immunostimulatory nucleic acid is reduced sufficiently, it is possible that the immunostimulatory nucleic acid is administered as frequently as the **asthma**/allergy medicament, albeit at a reduced dose.

DETD [0180] In other aspects, the invention relates to kits that are useful in the treatment of **asthma** and/or allergy. One kit of the invention includes a sustained release vehicle containing an immunostimulatory nucleic acid and a container housing an **asthma** /allergy medicament and instructions for timing of administration of the immunostimulatory nucleic acid in the **asthma**/allergy medicament. A sustained release vehicle is used herein in accordance with its prior art meaning of any device which slowly. . .

DETD [0182] The **asthma**/allergy medicament is housed in at least one container. The container may be a single container housing all of the **asthma**/allergy medicament together or it may be multiple containers or chambers housing individual dosages of the **asthma** /allergy medicament, such as a blister pack. The kit also has instructions for timing of administration of the **asthma** /allergy medicament. The instructions would direct the subject having **asthma**/allergy or at risk of **asthma**/allergy to take the **asthma**/allergy medicament at the appropriate time. For instance, the appropriate time for delivery of the medicament may be as the symptoms. . .

DETD . . . of the invention includes at least one container housing an immunostimulatory nucleic acid and at least one container housing an **asthma**/allergy medicament and instructions for administering the compositions in effective amounts for inducing a synergistic immune

response in the subject. The immunostimulatory nucleic acid and **asthma**/allergy medicament may be housed in single containers or in separate compartments or containers, such as single dose compartments. The instructions in the kit direct the subject to take the immunostimulatory nucleic acid and the **asthma**/allergy medicament in amounts which will produce a synergistic immune response. The drugs may be administered simultaneously or separately as long. . .

DETD [0184] In other aspects of the invention, a composition is provided. The composition includes an immunostimulatory nucleic and an **asthma**/allergy medicament formulated in a pharmaceutically-acceptable carrier and present in the composition in an effective amount for preventing or treating an immune or inflammatory response associated with exposure to a mediator of **asthma** or allergy. The effective amount for preventing or treating an immune or inflammatory response is that amount which prevents, inhibits. . . the induction of the immune or inflammatory response or prevents an increase in the immune or inflammatory response associated with **asthma** or allergy. An immune or inflammatory response associated with **asthma** or allergy includes an induction in IgE, an increase in Th2 cytokines, etc. A mediator of **asthma** or allergy includes **asthma** initiators and allergens. An example of a composition is one which comprises an immunostimulatory nucleic acid, such as a CpG nucleic acid, and an **asthma**/allergy medicament, such as an anti-IgE agent ~~(e.g., an anti-IgE antibody or antibody fragment). Such a composition~~ can be administered to. . .

DETD . . . methods as are well-known in the art is well within the capabilities of the ordinarily skilled artisan. Most of the **asthma**/allergy medicaments have been identified. These amounts can be adjusted when they are combined with immuno-stimulatory nucleic acids by routine experimentation.

DETD [0187] **Asthma**/allergy medicaments and immunostimulatory nucleic acids can be administered by any ordinary route for administering medications. Preferably, they are inhaled, ingested. . .

DETD [0189] For oral administration, the compounds (i.e., immunostimulatory nucleic acids, **asthma**/allergy medicament, other therapeutic agent) can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in. . .

DETD [0201] The immunostimulatory nucleic acids and **asthma**/allergy medicament may be administered per se (neat) or in the form of a pharmaceutically acceptable salt. When used in medicine. . .

DETD [0203] The pharmaceutical compositions of the invention contain an effective amount of an immunostimulatory nucleic acid and optionally **asthma**/allergy medicament and/or other therapeutic agents optionally included in a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier" means one or more compatible. . .

CLM What is claimed is:

1. A method for treating or preventing allergy or **asthma**, comprising administering to a subject a poly-G nucleic acid in an effective amount for treating or preventing allergy or **asthma**.

12. A method for treating or preventing **asthma** or allergy in a hypo-responsive subject, comprising: administering to a hypo-responsive subject having **asthma** or allergy or at risk of developing **asthma** or allergy an immunostimulatory nucleic acid in an effective amount for treating or preventing **asthma** or allergy.

13. The method of claim 12, wherein the hypo-responsive subject is hypo-responsive to an **asthma**/allergy medicament.

. . . claim 12, wherein the hypo-responsive subject is selected from the group consisting of a subject who is refractory to an **asthma**/allergy medicament, a subject who is a non-responder to an **asthma**/allergy medicament, an elderly subject and a neonatal

subject.

21. The method of claim 12, further comprising administering to the hypo-responsive subject an **asthma**/allergy medicament.

22. The method of claim 21, wherein the **asthma**/allergy medicament is administered in a sub-therapeutic amount.

23. The method of claim 21, wherein the **asthma**/allergy medicament is an **asthma** medicament.

24. The method of claim 21, wherein the **asthma**/allergy medicament is an allergy medicament.

25. The method of claim 21, wherein the **asthma**/allergy medicament is selected from the group consisting of a steroid and an immunomodulator.

30. The method of claim 21, wherein the **asthma**/allergy medicament is a medicament selected from the group consisting of a PDE-4 inhibitor, a bronchodilator/beta-2 agonist, a K.sup.+ channel opener,. . .

31. The method of claim 30, wherein the bronchodilator/beta-2 agonist is selected from the group consisting of salmeterol, **salbutamol**, ~~terbutaline, D2522/formoterol, fenoterol and orciprenaline.~~

32. The method of claim 21, wherein the **asthma**/allergy medicament is a medicament selected from the group consisting of an anti-histamine and a prostaglandin inducer.

35. The method of claim 21, wherein the immunostimulatory nucleic acid is administered concurrently with the **asthma**/allergy medicament.

36. A method for preventing **asthma** or allergy in a subject at risk of developing **asthma** or allergy, comprising: administering to a subject at risk of developing **asthma** or allergy an effective amount of an immunostimulatory nucleic acid substantially prior to an asthmatic or an allergic event.

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SUMM . . . of treating diseases and conditions of the upper and lower airway passages and the lungs. These conditions include, for example, **asthma** and rhinitis. One such technique involves administering certain pharmacologically active agents or drugs such as, for example, mometasone furoate, topically. . .

SUMM . . . when administering OTC nasal sprays, variation should be minimized where possible when administering prescription medications for such serious conditions as **asthma**. The dangers of over-medicating or under-medicating and the consequences of such unwanted deviation can be profound. The problem becomes even. . .

DETD . . . topically. Particularly preferred pharmacologically active agents in accordance with the present invention include, without limitation, corticosteroids such as: mometasone furoate; **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; (22R)-6.alpha., 9.alpha.-difluoro-11.beta.,21-dihydroxy-16.alpha.,17.alpha.-propylmethylenedioxy-4-pregnen-3,20-dione; tipredane and the like. .beta.-agonists (including .beta..sub.1 and .beta..sub.2-agonists) including, without limitation, **salbutamol** (albuterol), terbutaline, salmeterol, and bitolterol may also be administered. Formoterol (also known as eformoterol) e.g., as the fumarate or tartrate,. . .

DETD . . . results. Such inhalers include, without limitation, Schering's inhaler as identified above, Diskhaler (Allen & Hanburys), Accuhaler (Allen & Hanburys), Diskus (**Glaxo**), Spiros (Dura), Easyhaler (Orion), Cyclohaler (Pharmachemie), Cyclovent (Pharmachemie), Rotahaler (**Glaxo**), Spinhaler (Fisons), FlowCaps(Hovione), Turbospin (PH&T), Turbohaler (Astra), EZ Breath (Norton Healthcare/IVAX), MIAT-HALER (Miat), Pulvinal (Chiesi), Ultrahaler (Fisons/Rhone Poulenc Rorer), MAG-Haler. . .

CLM What is claimed is:

. . . claim 2, wherein said pharmacologically active agent comprises at least one member selected from the group consisting of: mometasone furoate; **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; **salbutamol**; albuterol; terbutaline; salmeterol; bitolterol; ipratropium bromide; oxitropium bromide; sodium cromoglycate; nedocromil sodium; zafirlukast; pranlukast; formoterol; eformoterol; bambuterol; fenoterol; clenbuterol; procaterol;. . .

. . . claim 46, wherein said pharmacologically active agent comprises at least one member selected from the group consisting of: mometasone furoate; **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; **salbutamol**; albuterol; terbutaline; salmeterol; bitolterol; ipratropium bromide; oxitropium bromide; sodium cromoglycate; nedocromil sodium; zafirlukast; pranlukast; formoterol; eformoterol; bambuterol; ~~fenoterol; clenbuterol; procaterol;~~. . .

. . . claim 53, wherein said pharmacologically active agent comprises at least one member selected from the group consisting of: mometasone furoate; **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; **salbutamol**; albuterol; terbutaline; salmeterol; bitolterol; ipratropium bromide; oxitropium bromide; sodium cromoglycate; nedocromil sodium; zafirlukast; pranlukast; formoterol; eformoterol; bambuterol; fenoterol; clenbuterol; procaterol;. . .

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SUMM . . . airways and other inflammatory diseases. Of particular importance as an object of these treatment combinations are the obstructive airways diseases **asthma**, chronic obstructive pulmonary disease (COPD), and other obstructive airways diseases exacerbated by heightened bronchial reflexes, inflammation, bronchial hyper-reactivity and bronchospasm,. . .

SUMM . . . particular, the combinations of compounds of the present invention are useful in the treatment of respiratory diseases and conditions comprising: **asthma**, acute respiratory distress syndrome, chronic pulmonary inflammatory disease, bronchitis, chronic bronchitis, chronic obstructive pulmonary (airway) disease, and silicosis; or immune. . .

SUMM . . . the present invention is concerned and which are used for the treatment of obstructive airways and other inflammatory diseases, especially **asthma**, COPD, and other obstructive airways diseases exacerbated by bronchial hyper-reactivity and bronchospasm, comprise the following: an adenosine A.sub.2A receptor agonist. . .

SUMM [0012] Activated eosinophils transmigrate into tissues and cause cellular damage and inflammation in such diseases as allergic and non-allergic **asthma**, allergic rhinitis, and atopic dermatitis. NECA inhibits zymosan-stimulated oxidative activity in guinea pig eosinophils suggesting an A.sub.2A mediated process. Thus,. . .

SUMM [0017] WO 99/67263 (Allen et al.) assigned to **Glaxo** Group Ltd. and published on Dec. 29, 1999 discloses anti-inflammatory adenosine A.sub.2A receptor agonists which inhibit leukocyte recruitment and activation,. . .

SUMM . . . that the adenosine A.sub.2A receptor agonists may be used in combination with other therapeutic such as corticosteroids, e.g., fluticasone propionate, **beclomethasone dipropionate**,

mometasone furoate, triamcinolone acetonide, or budesonide; NTHEs, e.g., sodium cromoglycate; P-adrenergic agents, e.g., salmeterol, **salbutamol**, formoterol, fenoterol, or terbutaline; and anti-infective agents, e.g., antibacterials or antivirals.

SUMM . . . history of use in the treatment of chronic airway diseases characterized by partially reversible airway narrowing such as COPD and **asthma** and were used as bronchodilators before the advent of epinephrine. They were thereafter supplanted by .beta.-adrenergic agents and methylxanthines. However,. . .

SUMM . . . anti-cholinergic agent, an anti-histaminic agent or a spasmolytic agent, in particular bronchoconstriction in a number of pulmonary diseases such as **asthma**. The above-mentioned methylecgonidine and its derivatives and epoxide analogs may be represented by Formulas (1.0.6) and (1.0.7), respectively: ##STR9##

SUMM . . . with novel combinations of therapeutic agents which are useful in the treatment of obstructive airways and other inflammatory diseases, especially **asthma**, COPD, and other obstructive airways diseases exacerbated by bronchial hyper-reactivity and bronchospasm. The novel combinations comprise the following: (i) an. . .

SUMM . . . The present invention is concerned with the above-described method of treatment wherein the obstructive airways or other inflammatory disease comprises **asthma**, chronic obstructive pulmonary disease (COPD), and other obstructive airways diseases exacerbated by bronchial hyper-reactivity and bronchospasm.

SUMM . . . heretofore to be useful as monotherapy for the treatment of obstructive airways and other inflammatory diseases, including especially COPD and **asthma**.

SUMM . . . defined herein to be one which has therapeutic activity in treating obstructive airways and other inflammatory diseases, especially COPD and **asthma**, when administered to a patient by means of inhalation. Within the scope of this group of adenosine A.sub.2A receptor agonist. . .

SUMM . . . that may be treated using the novel combinations of compounds of the present invention include but are not limited to **asthma**; chronic or acute bronchoconstriction; bronchitis; chronic bronchitis; small airways obstruction; emphysema; chronic obstructive pulmonary disease (COPD); COPD that has chronic. . .

SUMM [0377] **Asthma**

SUMM [0378] One of the most important respiratory diseases treatable with the combinations of therapeutic agents of the present invention is **asthma**, a chronic, increasingly common disorder encountered worldwide and characterized by intermittent reversible airway obstruction, airway hyper-responsiveness and inflammation. The cause of **asthma** has yet to be determined, but the most common pathological expression of **asthma** is inflammation of the airways, which may be significant even in the airways of patients with mild **asthma**. This inflammation drives reflex airway events resulting in plasma protein extravasation, dyspnea, and bronchoconstriction. Based on bronchial biopsy and lavage studies, it has been clearly shown that **asthma** involves infiltration by mast cells, eosinophils, and T-lymphocytes into a patient's airways. Bronchoalveolar lavage (BAL) in atopic asthmatics shows activation. . .

SUMM [0379] The combinations of therapeutic agents of the present invention are useful in the treatment of atopic and non-atopic **asthma**. The term "atopy" refers to a genetic predisposition toward the development of type I (immediate) hypersensitivity reactions against common environmental antigens. The most common clinical manifestation is allergic rhinitis, while bronchial **asthma**, atopic dermatitis, and food allergy occur less frequently. Accordingly, the expression "atopic **asthma**" as used herein is intended to be synonymous with "allergic **asthma**", i.e., bronchial **asthma** which is an allergic manifestation in a sensitized person. The term "non-atopic **asthma**" as used herein is intended to refer to all

other **asthmas**, especially essential or "true" **asthma**
, which is provoked by a variety of factors, including vigorous
exercise, irritant particles, psychologic stresses, etc.

SUMM [0380] The use of the combinations of therapeutic agents of the present invention to treat atopic **asthma** or non-atopic **asthma**
, COPD or other chronic airways diseases may be established and
demonstrated by use of a number of different models of. . .

SUMM . . . Airway smooth muscle hypertrophy and hyperplasia can be modulated by cAMP, and these conditions are common morphological features of chronic **asthma**.

SUMM . . . progress of both the acute and the late bronchial responses over time approximates the time course observed in humans with **asthma**; moreover, the pharmacological modification of both the acute and late responses is similar to that found in man. The responses.
. .

SUMM . . . assay, based on the use of primates, is that described in Turner et al., "Characterization of a primate model of **asthma**
using anti-allergy/anti-**asthma** agents," Inflammation Research
45 239-245, 1996.

SUMM . . . or obstructive airways diseases or other conditions involving airways obstruction. In particular they are useful for the treatment of bronchial **asthma**.

SUMM . . . method of effecting bronchodilation in mammals; and in particular, to a method of treating obstructive or inflammatory airways ~~diseases, especially **asthma**, in a mammal subject in need~~
thereof, which method comprises administering to the subject mammal an
effective amount of a. . .

SUMM [0413] Obstructive or inflammatory airways diseases to which the present invention applies include **asthma**; pneumoconiosis; chronic eosinophilic pneumonia; chronic obstructive airways or pulmonary disease (COAD or COPD); and adult respiratory distress syndrome (ARDS), as. .
.

SUMM [0414] The combinations of therapeutic agents of the present invention are useful in the treatment of **asthma** of whatever type,
etiology, or pathogenesis; including intrinsic **asthma**
attributed to pathophysiologic disturbances, extrinsic **asthma**
caused by some factor in the environment, and essential **asthma**
of unknown or inapparent cause. The combinations of therapeutic agents of the present invention are useful in the treatment of allergic (atopic/bronchial/IgE-mediated) **asthma**; and they are useful as well in the treatment of non-atopic **asthma**, including e.g.
bronchitic, emphysematous, exercise-induced, and occupational
asthma; infective **asthma** that is a sequela to
microbial, especially bacterial, fungal, protozoal, or viral infection;
and other non-allergic **asthmas**, e.g., incipient **asthma**
(wheezy infant syndrome).

SUMM . . . useful in the treatment of pneumoconiosis of whatever type, etiology, or pathogenesis; including, e.g., aluminosis (bauxite workers' disease); anthracosis (miners' **asthma**); asbestosis
(steam-fitters' **asthma**); chalicosis (flint disease); ptilosis
caused by inhaling the dust from ostrich feathers; siderosis caused by the inhalation of iron particles; silicosis (grinders' disease);
byssinosis (cotton-dust **asthma**); and talc pneumoconiosis.

SUMM [0418] COPD is characterized by inflammation of the airways, as is the case with **asthma**, but the inflammatory cells that have been
found in the bronchoalveolar lavage fluid and sputum of patients
neutrophils rather than. . .

SUMM . . . bronchitis which is a syndrome marked by the development of symptoms of bronchospasm following respiratory tract infections in persons with **asthma**; productive bronchitis which is bronchitis associated with a productive cough; staphylococcus or streptococcal bronchitis which are caused by staphylococci or. . .

SUMM . . . The utility of the combinations of therapeutic agents of the present invention as bronchodilators or bronchospasmolytic agents for

treating bronchial **asthma**, chronic bronchitis and related diseases and disorder described herein, is demonstrable through the use of a number of different in. . .

SUMM [0431] There is a recognized link between allergic rhinitis and **asthma**. Allergic rhinitis is a frequent accompaniment to **asthma**, and it has been demonstrated that treating allergic rhinitis will improve **asthma**. Epidemiologic data has also been used to show a link between severe rhinitis and more severe **asthma**. For example, the compound D-22888, under preclinical development for the treatment of allergic rhinitis, has been shown to exhibit a. . .

SUMM . . . of systemic necrotizing vasculitis in which there is prominent lung involvement, generally manifested by eosinophilia, granulomatous reactions, and usually severe **asthma**. A related disorder is polyarteritis nodosa (PAN), which is marked by multiple inflammatory and destructive arterial lesions and is a. . .

SUMM . . . individual response of the patient being treated. Thus, for example, where the active ingredients are used to treat or prevent **asthma**, and are administered topically via aerosol inhalation into the lungs, from one to four doses consisting of actuations of a. . .

SUMM . . . in an ultrasonic nebulizer which incorporates a fine mesh screen into its design. A therapeutic quantity of a concentrated nanoparticulate **beclomethasone dipropionate** formulation can be aerosolized in less than two seconds.

SUMM . . . of vitamin E and/or a polyethyleneglycol fatty acid ester as the high HLB surfactant present in the formulation. For example, **beclomethasone dipropionate** monohydrate is dissolved in a 2:1 wt./wt. mixture of PEG-200 and a-tocopherol polyethylene glycol succinate and then diluted with water,. . .

SUMM . . . of a pharmaceutical substance which, when exposed to water vapor, gives off heat of <1.2 J/g. Examples are given of **salbutamol** sulfate (25%) and lactose (75%) conditioned with water at relative humidity 55-65%, of a non-conditioned micronized substance mixture (5-8 J/g),. . .

SUMM . . . of respiratory tract diseases. For example, a liposome suspension contains 95% egg phosphatidylcholine, 29.6 mg/mL; 95% egg phosphatidylglycerol, 0.9 mg/mL; **beclomethasone dipropionate**, 0.42 mg/mL; vitamin E, 0.172 mg/mL; Na.sub.2HPO.sub.4, 1.5 mg/mL; NaCl, 5.0 mg/mL; and water to 1.0 mL. The liposome suspension. . .

SUMM . . . a surface modifier on the surface thereof. An example of a nebulizer solution is one containing a suspension of 2.5% **beclomethasone dipropionate** in an aqueous solution of polyvinyl alcohol as a surface modifier. The nanoparticles have a particle size distribution of 0.26. . .

SUMM [0495] WO 96/22764 discloses pharmaceutical liposomes or dehydrated liposomes for use in the treatment of **asthma** by inhalation therapy. An example of a nebulizer solution is one containing 9.alpha.-chloro-6.alpha.-fluoro-11.beta.-hydroxy-16.alpha.-methyl-3-oxo-17.alpha.-propionyloxyandrosta-1,4-diene-17.beta.-carboxylate and one or more synthetic phospholipids, especially. . .

CLM What is claimed is:

3. The pharmaceutical composition according to one of claims 1 or 2, wherein the obstructive airways disease is **asthma**, COPD, or other obstructive airways disease exacerbated by heightened bronchial reflexes, inflammation, bronchial hyper-reactivity and bronchospasm.

16. The method of treatment according to one of claims 14 or 15, wherein the obstructive airways disease is **asthma**, COPD, or other obstructive airways disease exacerbated by heightened bronchial reflexes, inflammation, bronchial hyper-reactivity and bronchospasm.

26. The pharmaceutical composition according to one of claims 24 or 25,

wherein the obstructive airways disease is **asthma**, COPD, or other obstructive airways disease exacerbated by heightened bronchial reflexes, inflammation, bronchial hyper-reactivity and bronchospasm.

L9 ANSWER 15 OF 28 USPATFULL on STN

SUMM . . . is an important means of treating a variety of conditions, including such common local conditions as cystic fibrosis, pneumonia, bronchial **asthma** and chronic obstructive pulmonary disease and some systemic conditions, including hormone replacement, pain management, immune deficiency, erythropoiesis, diabetes, etc. Steroids,. . .

DETD Particularly suitable medicaments or drugs include albuterol (also known as **salbutamol**), atropine, beclomethasone, esters of beclomethasone, such as its monopropionate and dipropionate, budesonide, cromolyn, epinephrine, ephedrine, fentanyl, flunisolide, formoterol, ipratropium bromide,. . .

DETD . . . include but are not limited to Sumiferon RTM interferon alpha-n1 available from Sumitomo, Japan; Welfferong interferon alpha-n1 (Ins) available from **Glaxo**-Wellcome Ltd., London, Great Britain; and Alferon RTM interferon alpha-n3 available from the Purdue Frederick Co., Norwalk, Conn.

CLM What is claimed is:

. . . as defined in claim 1 wherein said medicament is selected from the ~~group consisting of albuterol, atropine, beclomethasone, beclomethasone~~ monopropionate, **beclomethasone dipropionate**, budesonide, cromolyn, epinephrine, ephedrine, fentanyl, flunisolide, formoterol, ipratropium bromide, isoproterenol, pirbuterol, prednisone, triamcinolone acetonide, salmeterol, amiloride, fluticasone, fluticasone esters, (-)4-amino-3,5-dichloro-.alpha.-[[[6(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzene-methanol. . .

L9 ANSWER 16 OF 28 USPATFULL on STN

SUMM . . . derivatives which are useful for the treatment of inflammatory diseases are described in International Patent Application Nos. WO94/17090, WO96/02553, WO96/02543 (**Glaxo** Group). Substituted 4'-carboxamidoadenosine derivatives useful in the treatment of dementia are described in AU 8771946 (Hoechst Japan). Substituted 4'-hydroxymethyl adenosine. . .

SUMM . . . oxazolyl or isoxazolyl and the use of such compounds for the treatment of disorders involving cytokines in humans. WO 98/28319 (**Glaxo** Group Limited) was published subsequent to the earliest priority date of this application and describes 4'-substituted tetrazole 2-(purin-9-yl)-tetrahydrofuran-3,4-diol derivatives;

SUMM . . . effects include diseases of the respiratory tract such as adult respiratory distress syndrome (ARDS), bronchitis (including chronic bronchitis), cystic fibrosis, **asthma** (including allergen-induced asthmatic reactions), emphysema, rhinitis and septic shock. Other relevant disease states include diseases of the gastrointestinal tract such. . .

SUMM . . . may also be used in combination with other therapeutic agents, for example anti-inflammatory agents (such as corticosteroids (e.g. fluticasone propionate, **beclomethasone dipropionate**, mometasone furoate, triamcinolone acetonide or budesonide) or NSAIDs (eg sodium cromoglycate)) or beta adrenergic agents (such as salmeterol, **salbutamol**, formoterol, fenoterol or terbutaline and salts thereof) or antiinfective agents (eg antibiotics, antivirals).

L9 ANSWER 17 OF 28 USPATFULL on STN

SUMM . . . derivatives which are useful for the treatment of inflammatory diseases are described in International Patent Application Nos. WO94/17090, WO96/02553, WO96/02543 (**Glaxo** Group). Substituted 4'-carboxamidoadenosine derivatives useful in the treatment of dementia are described in AU 8771946 (Hoechst Japan). Substituted

4'-hydroxymethyl adenosine. . .

SUMM . . . effects include diseases of the respiratory tract such as adult respiratory distress syndrome (ARDS), bronchitis (including chronic bronchitis), cystic fibrosis, **asthma** (including allergen-induced asthmatic reactions), chronic obstructive pulmonary disease (COPD), emphysema, rhinitis and septic shock. Other relevant disease states include diseases. . .

SUMM [0149] Diseases of principal interest include **asthma** and COPD.

SUMM . . . may also be used in combination with other therapeutic agents, for example anti-inflammatory agents (such as corticosteroids (eg fluticasone propionate, **beclomethasone dipropionate**, mometasone furoate, triamcinolone acetonide or budesonide) or NSAIDs (eg sodium cromoglycate)) or beta adrenergic agents (such as salmeterol, **salbutamol**, formoterol, fenoterol or terbutaline and salts thereof) or antiinfective agents (eg antibiotics, antivirals).

L9 ANSWER 18 OF 28 USPATFULL on STN

SUMM [0004] A disturbance of the protease/protease inhibitor balance can lead to protease-mediated tissue destruction, including emphysema, **asthma**, arthritis, glomerulonephritis, periodontitis, muscular dystrophy, tumor invasion and various other pathological conditions. In certain situations, e.g., severe pathological processes such. . .

SUMM . . . pulmonary administration of pharmaceutical compositions containing low molecular weight drugs, most notably in the area of ~~beta-androgenic antagonists to treat **asthma**. Other low~~ molecular weight, non-proteinaceous compounds, including corticosteroids and cromolyn sodium, have been administered systemically via pulmonary absorption. Not all. . .

SUMM . . . by leukocyte- and mast cell-mediated disorders. The compositions would be particularly beneficial in the treatment of inflammatory airway diseases such **asthma**, chronic bronchitis, chronic obstructive pulmonary disease, emphysema, as well as other forms of bronchoconstriction, of acute respiratory failure, or of. . .

DETD . . . however, provides a dry powder protein pharmaceutical composition suitable for inhalation therapy and the treatment of pulmonary conditions such as **asthma**. The composition is uniquely formulated and produced such that the protein therapeutic agent retains its biological activity upon deposition to. . .

DETD . . . counteracting bronchoconstriction or the development of airway hyperresponsiveness. Types of drugs known to be useful in the inhalation treatment of **asthma** include respiratory NSAIDs (cromolyn sodium, nedocromil, etc.); anticholinergic agents (such as atropine and ipratropium bromide); beta 2 agonists (such as adrenaline, isoproterenol, ephedrine, **salbutamol**, terbutaline, orciprenaline, fenoterol, and isoetharine), methylxanthines (such as theophylline); calcium-channel blockers (such as verapamil); and glucocorticoids (such as prednisone, prednisolone, dexamethasone, **beclomethasone dipropionate**, and beclomethasone valerate), as described in Chapter 39 of Principles of Medical Pharmacology, Fifth Edition, Kalant and Roschlau, Ed. (B.. . .

DETD . . . of combination compositions include inhibitors of TNF.alpha., inhibitors of IgE synthesis or activity, inhibitors of cytokines or chemokines associated with **asthma** pathogenesis, other protease inhibitors, and heparin. Additional agents which can be used in combination with SLPI include monoclonal antibodies, soluble. . .

DETD . . . pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, **asthma**, status asthmaticus, or hypoxia (including that which may occur during one-lung anesthesia). In addition, the compositions may be used in. . .

DETD . . . amount of SLPI will depend on the particular disease state or condition being treated. For instance, in the case of **asthma**, a therapeutically effective amount of SLPI will be an amount sufficient

to inhibit bronchoconstriction and development of airway hyperreactivity to provide effective reduction of **asthma** symptomology. The therapeutically effective amount will depend on a variety of factors which the knowledgeable practitioner will take into account. . .

DETD . . . are incorporated herein by reference. Additional devices are exemplified by those used by Dura Pharmaceuticals, Inc., San Diego, Calif., and **Glaxo** Inc., Research Triangle Park, N.C.

DETD . . . appropriate steroid or antibiotic. SLPI dry powder pharmaceutical compositions are advantageously used in the treatment of pulmonary conditions such as **asthma**. In particular, the SLPI dry powder pharmaceutical compositions may be used to inhibit pulmonary mucous production/secretion, increase mucous velocity in. . .

DETD . . . human airway which exhibits broad spectrum inhibitory activity against mast cell and leukocyte serine proteases implicated in the pathogenesis of **asthma**. To assess the potential therapeutic utility of SLPI in **asthma**, its effects on antigen-induced pulmonary responses, as well as pathologic changes of the airways associated with **asthma**, were evaluated. SLPI inhibited early and late phase bronchoconstriction in sheep and the development of airway hyperreactivity in guinea pigs. . . velocity in sheep. These results provide evidence that pulmonary SLPI delivery is suitable for therapeutic intervention against the pathophysiology of **asthma** as well as its underlying pathology.

DETD [0142] **Asthma** is a chronic pulmonary disorder characterized by two key pathophysiologic components: recurrent bronchoconstriction and development of airway hyperresponsiveness to allergic and environmental stimuli. These physiologic responses are manifest as cough, wheezing, and shortness of breath (National **Asthma** Education and Prevention Program. Expert panel report II: Guidelines for the diagnosis and management of **asthma**. 1997). While there has been great success in the development of symptomatic therapies for **asthma**, the concept that these pathophysiologic responses occur within airways that have been profoundly modified has not been fully addressed. Such. . . fibrosis, edema, and smooth muscle hypertrophy (Dunnill, M. S. J. Clin. Pathol. 13:27-33, 1960.) Despite the various therapeutic approaches available, **asthma** continues to represent a significant unmet medical need, particularly for patients with moderate and severe **asthma**. The population of patients with severe **asthma** continues to grow and the rate of hospitalization among patients with **asthma** remains high. It has been hypothesized that current therapies fail to address a fundamental component of **asthma** pathogenesis.

DETD [0143] Emerging evidence suggests that serine proteases play a key role in the pathogenesis of **asthma** (Caughey, G. Am. J Physiol. (Lung Cell. Mol. Physiol.), 257:L39-L46, 1989; Walls, A. F. 1994. **Asthma** and Rhinitis, 801-824, edited by Busse, W. W. and S. T. Holgate. Boston: Blackwell Scientific Publications). Mast cell and leukocyte. . . 1995). In addition, patients with reduced anti-protease activity as a result of .alpha.-1-antitrypsin deficiency have an increased propensity to develop **asthma** (Eden, et al. Am. J Respir. Crit. Care Med., 156:68-74, 1997). In animal studies, instillation of elastase (Suzuki, et al.. . . 1996; Walls, et al. Int. Arch. Allergy Immunol., 107:372-373, 1995) have also been implicated in promoting airway pathology associated with **asthma**. In addition, tryptase stimulates allergic mediator release from mast cells (He, et al. Eur. J. Pharmacol., 328:89-97, 1997). These observations support the contribution of serine proteases to both the pathophysiology and airway pathology associated with **asthma** and indicate that the inhibition of mast cell and leukocyte serine proteases represent an important new approach for the treatment of **asthma**.

DETD . . . biochemical profile, the following studies were conducted to evaluate the efficacy of SLPI against the pathophysiology and pathology associated with **asthma**.

DETD . . . protease inhibitory activity of SLPI is summarized in Table 4. SLPI exhibits potent broad-spectrum inhibition of serine proteases implicated in **asthma** pathology, including cathepsin G, elastase, and tryptase. In contrast, factor Xa, kallikreins, thrombin, and plasmin were unaffected by SLPI at. . .

DETD [0174] SLPI represents a novel therapeutic approach to the treatment of **asthma**. SLPI is a broad spectrum serine protease inhibitor naturally produced in the human airway. These studies demonstrated that SLPI can. . .

DETD [0175] While **asthma** has not been associated with a deficiency of SLPI, mounting evidence demonstrates the development of a protease-antiprotease imbalance in the. . . SLPI inactivation. The resultant increase in proteolytic activity contributes to airway pathophysiology as well as the airway remodeling associated with **asthma**.

DETD . . . reports suggest that inhibition of a single serine protease is not sufficient to impact that pathophysiology and pathology associated with **asthma**. In sheep, .alpha..sub.1-protease inhibitor has been shown to prevent antigen-induced mucociliary dysfunction through inhibition of elastase (O'Riordan, et al., Am.. . .

DETD . . . is increased recognition of the need for agents which prevent airway remodeling to complement symptomatic relief in the treatment of **asthma**. The ability of SLPI to prevent mucociliary dysfunction represents an intervention against a critical pathologic change of the asthmatic airway.. . .

L9 ANSWER 19 OF 28 USPATFULL on STN

SUMM . . . derivatives which are useful for the treatment of inflammatory diseases are described in international Patent Application Nos. WO94/17090, WO96/02553, WO96/02543 (**Glaxo** Group). Substituted 4'-carboxamidoadenosine derivatives useful in the treatment of dementia are described in AU 8771946 (Hoechst Japan). Substituted 4'-hydroxymethyl adenosine. . .

SUMM . . . oxazolyl or isoxazolyl and the use of such compounds for the treatment of disorders involving cytokines in humans. WO 98/28319 (**Glaxo** Group Limited) was published subsequent to the earliest priority date of this application and describes 4'-substituted tetrazole 2-(purin-9-yl)-tetrahydrofuran-3,4-diol derivatives.

SUMM . . . effects include diseases of the respiratory tract such as adult respiratory distress syndrome. (ARDS), bronchitis (including chronic bronchitis), cystic fibrosis, **asthma** (including allergen-induced asthmatic reactions), chronic obstructive pulmonary disease (COPD), emphysema, rhinitis and septic shock. Other relevant disease states include diseases. . .

SUMM Diseases of principal interest include **asthma** and COPD.

SUMM . . . may also be used in combination with other therapeutic agents, for example anti-inflammatory agents (such as corticosteroids (eg fluticasone propionate, **beclomethasone dipropionate**, mometasone furoate, triamcinolone acetonide or budesonide) or NSAIDs (eg sodium cromoglycate)) or beta adrenergic agents (such as salmeterol, **salbutamol**, formoterol, fenoterol or terbutaline and salts thereof) or antiinfective agents (eg antibiotics, antivirals).

L9 ANSWER 20 OF 28 USPATFULL on STN

SUMM . . . derivatives which are useful for the treatment of inflammatory diseases are described in International Patent Application Nos. WO94/17090, WO96/02553, WO96/02543 (**Glaxo** Group) Substituted 4'-carboxamidoadenosine derivatives useful in the treatment of dementia are described in AU 8771946 (Hoechst Japan). Substituted 4'-hydroxymethyl adenosine. . .

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L9 ANSWER 21 OF 28 USPATFULL on STN

SUMM . . . of treating diseases and conditions of the upper and lower airway passages and the lungs. These conditions include, for example, **asthma** and rhinitis. One such technique involves administering certain pharmacologically active agents or drugs such as, for example, mometasone furoate, topically. . .

SUMM . . . when administering OTC nasal sprays, variation should be minimized where possible when administering prescription medications for such serious conditions as **asthma**. The dangers of over-medicating or under-medicating and the consequences of such unwanted deviation can be profound. The problem becomes even. . .

DETD . . . topically. Particularly preferred pharmacologically active agents in accordance with the present invention include, without limitation, ~~corticosteroids such as: mometasone furoate;~~ **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; (22R)-6.alpha.,9.alpha.-difluoro-11.beta.,21-dihydroxy-16.alpha.,17.alpha.-propylmethylenedioxy-4-pregnen-3,20-dione; tipredane and the like. .beta.-agonists (including .beta..sub.1 and .beta..sub.2-agonists) including, without limitation, **salbutamol** (albuterol), terbutaline, salmeterol, and bitolterol may also be administered. Formoterol (also known as eformoterol) e.g., as the fumarate or tartrate,. . .

DETD . . . results. Such inhalers include, without limitation, Schering's inhaler as identified above, Diskhaler (Allen & Hanburys), Accuhaler (Allen & Hanburys), Diskus (**Glaxo**), Spiros (Dura), Easyhaler (Orion), Cyclohaler (Pharmachemie), Cyclovent (Pharmachemie), Rotahaler (**Glaxo**), Spinhaler (Fisons), FlowCaps(Hovione), Turbospin (PH&T), Turbohaler (Astra), EZ Breath (Norton Healthcare/1VAX), MIAT-HALER (Miat), Pulvinal (Chiesi), Ultrahaler (Fisons/Rhone Poulenc Rorer), MAG-Haler. . .

CLM What is claimed is:

. . . claim 2, wherein said pharmacologically active agent comprises at least one member selected from the group consisting of: mometasone furoate; **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; **salbutamol**; albuterol; terbutaline; salmeterol; bitolterol; ipratropium bromide; oxitropium bromide; sodium cromoglycate; nedocromil sodium; zafirlukast; pranlukast; formoterol; eformoterol; bambuterol; fenoterol; clenbuterol; procaterol;. . .

. . . claim 46, wherein said pharmacologically active agent comprises at least one member selected from the group consisting of: mometasone furoate; **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; **salbutamol**; albuterol; terbutaline; salmeterol; bitolterol; ipratropium bromide; oxitropium bromide; sodium cromoglycate; nedocromil sodium; zafirlukast; praniukast; formoterol; eformoterol; bambuterol; fenoterol; clenbuterol; procaterol;. . .

. . . claim 53, wherein said pharmacologically active agent comprises at least one member selected from the group consisting of: mometasone furoate; **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; **salbutamol**; albuterol; terbutaline; salmeterol; bitolterol; ipratropium bromide; oxitropium bromide; sodium cromoglycate; nedocromil

sodium; zafirlukast; pranlukast; formoterol; eformoterol; bambuterol; fenoterol; clenbuterol; procaterol;. . .

L9 ANSWER 22 OF 28 USPATFULL on STN

DETD . . . invention include anti-allergics, peptides and proteins, bronchodilators and anti-inflammatory steroids for use in the treatment of respiratory disorders such as **asthma** by inhalation therapy.

DETD . . . invention include mast cell inhibitors (anti-allergics), bronchodilators, and anti-inflammatory steroids for use in the treatment of respiratory disorders such as **asthma** by inhalation therapy, for example cromoglycate (e.g. the sodium salt), and albuterol (e.g. the sulfate salt). For systemic delivery (e.g.. . .

DETD . . . cromolyn sodium; antiinfectives, e.g. cephalosporins, macrolides, quinolines, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. fluticasone propionate, **beclomethasone dipropionate**, flunisolide, budesonide, tripedane, cortisone, prednisone, prednisilone, dexamethasone, betamethasone, or triamcinolone acetonide; antitussives, e.g. noscapine; bronchodilators, e.g. ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, **salbutamol**, albuterol, salmeterol, terbutaline; diuretics, e.g. amiloride; anticholinergics, e.g. ipatropium, atropine, or oxitropium; lung surfactants e.g. Surfaxin, Exosurf, Survanta; xanthines, e.g.. . .

DETD [0159] Perforated microstructures comprising **beclomethasone dipropionate** (BDP) particles were prepared by a spray-drying technique with a B-191 Mini Spray-Drier (Buchi, Flawil, Switzerland) under the following spray. . .

DETD . . . particle size distribution trends indicated that the deposition on the filter was negligibly small. Methanol was used for extraction of **beclomethasone dipropionate** and triamcinolone acetonide. Deionized water was used for albuterol sulfate, cromolyn sodium, and DNase I. For albuterol MDIs, 0.5 ml. . .

DETD . . . quantitated by absorption spectroscopy (Beckman DU640 spectrophotometer) relative to an external standard curve with the extraction solvent as the blank. **Beclomethasone dipropionate** and triamcinolone acetonide were quantitated by measuring the absorption of the plate extracts at 238 nm Albuterol MDIs were quantified. . .

DETD . . . 48.5 .+-. 0.7
(3M Pharm.) (2.1 .+-. 0.3)
108 .mu.g dose
Ventolin .RTM., CFC 2.2 .+-. 0.2 58.9 43.5 .+-. 2.6 45.3 .+-. 3.3
(**Glaxo** Wellc- (1.9 .+-. 0.1)
ome) 108 .mu.g dose
Perforated 3.1 .+-. 0.2 14.9 79.3 .+-. 0.6 57.1 .+-. 5.7
microstructures, (1.7 .+-. 0.01)
HFA. . .

DETD Andersen Cascade Impactor Results for **Beclomethasone Dipropionate** MDI Formulations

DETD . . . an analogous spray-dried hollow porous powder prepared according to Examples V and IX are listed below in Table V.

TABLE V

Beclomethasone Dipropionate MDIs

	MMAD (GSD)	Throat Deposition, .mu.g	Fine particle fraction, %	Fine Part-icle Dose, .mu.g
Vanceril .RTM. CFC,	3.47	32	35. . .	

DETD . . . formulated with spray dried hollow porous particles were found to have superior aerosol performance compared with Vanceril. The spray dried **beclomethasone dipropionate** formulations

possessed a substantially higher fine particle fraction (.about.56% vs. 35%), and significantly lower throat deposition (.about.3-fold) than Vanceril. The. . .

L9 ANSWER 23 OF 28 USPATFULL on STN

SUMM . . . of treating diseases and conditions of the upper and lower airway passages and the lungs. These conditions include, for example, **asthma** and rhinitis. One such technique involves administering certain pharmacologically active agents or drugs such as, for example, mometasone furoate, topically. . .

SUMM . . . when administering OTC nasal sprays, variation should be minimized where possible when administering prescription medications for such serious conditions as **asthma**. The dangers of over-medicating or under-medicating and the consequences of such unwanted deviation can be profound. The problem becomes even. . .

DETD . . . topically. Particularly preferred pharmacologically active agents in accordance with the present invention include, without limitation, corticosteroids such as: mometasone furoate; **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; (22R)-6.alpha.,9.alpha.-difluoro-11.beta.,21-dihydroxy-16.alpha.,17.alpha.-propylmethylenedioxy-4-pregnen-3,20-dione; tipredane and the like. .beta.-agonists (including .beta..sub.1 and .beta..sub.2-agonists) including, without limitation, **salbutamol** (albuterol), terbutaline, salmeterol, and bitolterol may also be administered. Formoterol (also known as eformoterol) e.g., as the fumarate or tartrate,. . .

DETD . . . results. Such inhalers include, without limitation, Schering's inhaler as identified above, Diskhaler (Allen & Hanburys), Accuhaler (Allen & Hanburys), Diskus (**Glaxo**), Spiros (Dura), Easyhaler (Orion), Cyclohaler (Pharmachemie), Cyclovent (Pharmachemie), Rotahaler (**Glaxo**), Spinhaler (Fisons), FlowCaps(Hovione), Turbospin (PH&T), Turbohaler (Astra), EZ Breath (Norton Healthcare/IVAX), MIAT-HALER (Miat), Pulvinal (Chiesi), Ultrahaler (Fisons/Rhone Poulenc Rorer), MAG-Haler. . .

CLM What is claimed is:

. . . claim 2, wherein said pharmacologically active agent comprises at least one member selected from the group consisting of: mometasone furoate; **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; **salbutamol**; albuterol; terbutaline; salmeterol; bitolterol; ipratropium bromide; oxitropium bromide; sodium cromoglycate; nedocromil sodium; zafirlukast; pranlukast; formoterol; eformoterol; bambuterol; fenoterol; clenbuterol; procaterol;. . .

. . . claim 46, wherein said pharmacologically active agent comprises at least one member selected from the group consisting of: mometasone furoate; **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; **salbutamol**; albuterol; terbutaline; salmeterol; bitolterol; ipratropium bromide; oxitropium bromide; sodium cromoglycate; nedocromil sodium; zafirlukast; pranlukast; formoterol; eformoterol; bambuterol; fenoterol; clenbuterol; procaterol;. . .

. . . claim 53, wherein said pharmacologically active agent comprises at least one member selected from the group consisting of: mometasone furoate; **beclomethasone dipropionate**; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; **salbutamol**; albuterol; terbutaline; salmeterol; bitolterol; ipratropium bromide; oxitropium bromide; sodium cromoglycate; nedocromil sodium; zafirlukast; pranlukast; formoterol; eformoterol; bambuterol; fenoterol; clenbuterol; procaterol;. . .

L9 ANSWER 24 OF 28 USPATFULL on STN

SUMM [0004] A disturbance of the protease/protease inhibitor balance can lead to protease-mediated tissue destruction, including emphysema, **asthma**, arthritis, glomerulonephritis, periodontitis, muscular

dystrophy, tumor invasion and various other pathological conditions. In certain situations, e.g., severe pathological processes such. . .

SUMM . . . pulmonary administration of pharmaceutical compositions containing low molecular weight drugs, most notably in the area of beta-androgenic antagonists to treat **asthma**. Other low molecular weight, non-proteinaceous compounds, including corticosteroids and cromolyn sodium, have been administered systemically via pulmonary absorption. Not all. . .

SUMM . . . by leukocyte- and mast cell-mediated disorders. The compositions would be particularly beneficial in the treatment of inflammatory airway diseases such **asthma**, chronic bronchitis, chronic obstructive pulmonary disease, emphysema, as well as other forms of bronchoconstriction, of acute respiratory failure, or of. . .

DETD . . . however, provides a dry powder protein pharmaceutical composition suitable for inhalation therapy and the treatment of pulmonary conditions such as **asthma**. The composition is uniquely formulated and produced such that the protein therapeutic agent retains its biological activity upon deposition to. . .

DETD . . . counteracting bronchoconstriction or the development of airway hyperresponsiveness. Types of drugs known to be useful in the inhalation treatment of **asthma** include respiratory NSAIDs (cromolyn sodium, nedocromil, etc.); anticholinergic agents (such as atropine and ipratropium bromide); beta 2 agonists (such as adrenaline, isoproterenol, ephedrine, **salbutamol**, terbutaline, ~~orciprenaline, fenoterol, and isoetharine), methylxanthines~~ (such as theophylline); calcium-channel blockers (such as verapamil); and glucocorticoids (such as prednisone, prednisolone, dexamethasone, **beclomethasone dipropionate**, and beclomethasone valerate), as described in Chapter 39 of Principles of Medical Pharmacology, Fifth Edition, Kalant and Roschlau, Ed. (B.. . .

DETD . . . of combination compositions include inhibitors of TNF.alpha., inhibitors of IgE synthesis or activity, inhibitors of cytokines or chemokines associated with **asthma** pathogenesis, other protease inhibitors, and heparin. Additional agents which can be used in combination with SLPI include monoclonal antibodies, soluble. . .

DETD . . . pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, **asthma**, status asthmaticus, or hypoxia (including that which may occur during one-lung anesthesia). In addition, the compositions may be used in. . .

DETD . . . amount of SLPI will depend on the particular disease state or condition being treated. For instance, in the case of **asthma**, a therapeutically effective amount of SLPI will be an amount sufficient to inhibit bronchoconstriction and development of airway hyperreactivity to provide effective reduction of **asthma** symptomology. The therapeutically effective amount will depend on a variety of factors which the knowledgeable practitioner will take into account. . .

DETD . . . are incorporated herein by reference. Additional devices are exemplified by those used by Dura Pharmaceuticals, Inc., San Diego, Calif., and **Glaxo** Inc., Research Triangle Park, N.C.

DETD . . . appropriate steroid or antibiotic. SLPI dry powder pharmaceutical compositions are advantageously used in the treatment of pulmonary conditions such as **asthma**. In particular, the SLPI dry powder pharmaceutical compositions may be used to inhibit pulmonary mucous production/secretion, increase mucous velocity in. . .

DETD . . . human airway which exhibits broad spectrum inhibitory activity against mast cell and leukocyte serine proteases implicated in the pathogenesis of **asthma**. To assess the potential therapeutic utility of SLPI in **asthma**, its effects on antigen-induced pulmonary responses, as well as pathologic changes of the airways associated with **asthma**, were evaluated. SLPI inhibited early and late phase bronchoconstriction in sheep and the development of airway hyperreactivity in guinea pigs. . . velocity in sheep. These

results provide evidence that pulmonary SLPI delivery is suitable for therapeutic intervention against the pathophysiology of **asthma** as well as its underlying pathology.

DETD [0133] **Asthma** is a chronic pulmonary disorder characterized by two key pathophysiologic components: recurrent bronchoconstriction and development of airway hyperresponsiveness to allergic and environmental stimuli. These physiologic responses are manifest as cough, wheezing, and shortness of breath (National **Asthma** Education and Prevention Program. Expert panel report II: Guidelines for the diagnosis and management of **asthma**. 1997). While there has been great success in the development of symptomatic therapies for **asthma** , the concept that these pathophysiologic responses occur within airways that have been profoundly modified has not been fully addressed. Such. . . fibrosis, edema, and smooth muscle hypertrophy (Dunnill, M. S. J. Clin. Pathol. 13:27-33, 1960.) Despite the various therapeutic approaches available, **asthma** continues to represent a significant unmet medical need, particularly for patients with moderate and severe **asthma**. The population of patients with severe **asthma** continues to grow and the rate of hospitalization among patients with **asthma** remains high. It has been hypothesized that current therapies fail to address a fundamental component of **asthma** pathogenesis.

DETD [0134] Emerging evidence suggests that serine proteases play a key role in the pathogenesis of **asthma** (Caughey, G. Am. J. Physiol. ~~(Lung Cell. Mol. Physiol.), 257:L39-L46, 1989; Walls, A. F. 1994.~~ **Asthma** and Rhinitis, 801-824, edited by Busse, W. W. and S. T. Holgate. Boston: Blackwell Scientific Publications). Mast cell and leukocyte. . . 1995). In addition, patients with reduced anti-protease activity as a result of .alpha.-1-antitrypsin deficiency have an increased propensity to develop **asthma** (Eden, et al. Am. J. Respir. Crit. Care Med., 156:68-74, 1997). In animal studies, instillation of elastase (Suzuki, et al.. . . 1996; Walls, et al. Int. Arch. Allergy Immunol., 107:372-373, 1995) have also been implicated in promoting airway pathology associated with **asthma** . In addition, tryptase stimulates allergic mediator release from mast cells (He, et al. Eur. J. Pharmacol., 328:89-97, 1997). These observations support the contribution of serine proteases to both the pathophysiology and airway pathology associated with **asthma** and indicate that the inhibition of mast cell and leukocyte serine proteases represent an important new approach for the treatment of **asthma**.

DETD . . . biochemical profile, the following studies were conducted to evaluate the efficacy of SLPI against the pathophysiology and pathology associated with **asthma**.

DETD . . . protease inhibitory activity of SLPI is summarized in Table 4. SLPI exhibits potent broad-spectrum inhibition of serine proteases implicated in **asthma** pathology, including cathepsin G, elastase, and tryptase. In contrast, factor Xa, kallikreins, thrombin, and plasmin were unaffected by SLPI at. . .

DETD [0154] SLPI represents a novel therapeutic approach to the treatment of **asthma**. SLPI is a broad spectrum serine protease inhibitor naturally produced in the human airway. These studies demonstrated that SLPI can. . .

DETD [0155] While **asthma** has not been associated with a deficiency of SLPI, mounting evidence demonstrates the development of a protease-antiprotease imbalance in the. . . SLPI inactivation. The resultant increase in proteolytic activity contributes to airway pathophysiology as well as the airway remodeling associated with **asthma**.

DETD . . . reports suggest that inhibition of a single serine protease is not sufficient to impact that pathophysiology and pathology associated with **asthma**. In sheep, .alpha..sub.1-protease inhibitor has been shown to prevent antigen-induced mucociliary dysfunction through inhibition of elastase (O'Riordan, et al., Am.. . .

DETD . . . is increased recognition of the need for agents which prevent airway remodeling to complement symptomatic relief in the treatment of **asthma**. The ability of SLPI to prevent mucociliary dysfunction represents an intervention against a critical pathologic change of the asthmatic airway.. . .

L9 ANSWER 25 OF 28 USPATFULL on STN

DETD . . . invention include anti-allergics, peptides and proteins, bronchodilators and anti-inflammatory steroids for use in the treatment of respiratory disorders such as **asthma** by inhalation therapy.

DETD . . . invention include mast cell inhibitors (anti-allergics), bronchodilators, and anti-inflammatory steroids for use in the treatment of respiratory disorders such as **asthma** by inhalation therapy, for example cromoglycate (e.g. the sodium salt), and albuterol (e.g. the sulfate salt). For systemic delivery (e.g.. . .

DETD . . . cromolyn sodium; antiinfectives, e.g. cephalosporins, macrolides, quinolines, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. fluticasone propionate, **beclomethasone dipropionate**, flunisolide, budesonide, tripedane, cortisone, prednisone, prednisilone, dexamethasone, betamethasone, or triamcinolone acetonide; antitussives, e.g. noscapine; bronchodilators, e.g. ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, **salbutamol**, albuterol, salmeterol, terbutaline; diuretics, e.g. amiloride; anticholinergics, e.g. ipatropium, atropine, or oxitropium; lung surfactants e.g. Surfaxin, Exosurf, Survanta; xanthines, e.g.. . .

DETD Perforated microstructures comprising **beclomethasone dipropionate** (BDP) particles were prepared by a spray-drying technique with a B-191 Mini Spray-Drier (Buchi, Flawil, Switzerland) under the following spray. . .

DETD . . . particle size distribution trends indicated that the deposition on the filter was negligibly small. Methanol was used for extraction of **beclomethasone dipropionate** and triamcinolone acetonide. Deionized water was used for albuterol sulfate, cromolyn sodium, and DNase I. For albuterol MDIs, 0.5 ml. . .

DETD . . . quantitated by absorption spectroscopy (Beckman DU640 spectrophotometer) relative to an external standard curve with the extraction solvent as the blank. **Beclomethasone dipropionate** and triamcinolone acetonide were quantitated by measuring the absorption of the plate extracts at 238 nm Albuterol MDIs were quantified. . .

DETD . . . 48.5 .+-. 0.7
(3M Pharm.) (2.1 .+-. 0.3)
108 .mu.g dose
Ventolin .RTM., CFC 2.2 .+-. 0.2 58.9 43.5 .+-. 2.6 45.3 .+-. 3.3
(**Glaxo** Wellcome) (1.9 .+-. 0.1)
108 .mu.g dose
Perforated 3.1 .+-. 0.2 14.9 79.3 .+-. 0.6 57.1 .+-. 5.7
microstructures, HFA (1.7 .+-. 0.01)
(Alliance. . .

DETD Andersen Cascade Impactor Results for **Beclomethasone Dipropionate** MDI Formulations

DETD TABLE V

Beclomethasone Dipropionate MDIs

	MMAD (GSD)	Throat Deposition, .mu.g	Fine particle fraction, %	Fine Particle Dose, .mu.g
Vanceril .RTM., CFC	3.47	32	35. . .	

DETD . . . MDIs formulated with spray dried hollowporous particles were found to have superior aerosol performance compared with Vanceril. The spray dried **beclomethasone dipropionate** formulations possessed a substantially higher fine particle fraction (.about.56% vs.

35%), and significantly lower throat deposition (.about.3-fold) than Vanceril. The. . .

L9 ANSWER 26 OF 28 USPATFULL on STN

SUMM **Asthma** and other respiratory diseases are typically treated by the inhalation of an appropriate medicament for deposition into the lungs to. . .

SUMM . . . al. These patents show, respectively, an agglomerator-pelletizer apparatus and a wet granulator apparatus for preparing pellets or granules of the **asthma** medicament, disodium cromoglycate, which may then be placed inside of a capsule.

SUMM . . . is a screen mesh which is impregnated in spaced locations or interstices along its circumference with a dose of powdered **asthma** medicament, such as salmeterol hydroxynapthoate. During inhalation, air impinging on the powdered medicament impregnated into the interstices of the screen. . .

DRWD FIG. 7 is a photomicrograph of tumble-agglomerated medicament powder particles of the medicament, **beclomethasone dipropionate**; and

DETD The respirable powdered medicaments for inhalation therapy or systemic absorption via the respiratory tract to treat respiratory disorders such as **asthma**, bronchitis, chronic obstructive pulmonary diseases and chest infection may be selected from, but not limited to, the group consisting, for. . . cromoglycate, ketotifen or neodocromil; ~~antiinfectives e.g. cephalosporins, penicillins, stretomycin,~~ sulphonamides, tetracyclines and pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. fluticasone propionate, **beclomethasone dipropionate**, flunisolide, budesonide or triamcinolone acetonide; antitussives, e.g. noscapine; bronchodilators, e.g. salmeterol, salmbutamol, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine,. . . lower alkyl esters) or as solvates (e.g. hydrates) to optimise the activity and/or stability of the medicament. Preferred medicaments are **salbutamol**, salmeterol, fluticasone propionate, **beclomethasone dipropionate**, terbutaline, cromoglycate, budesonide, and triamcinolone acetonide and/or salts thereof.

DETD . . . of particles SM depends upon the drug used. For instance, SH, which is a common drug used for treatment of **asthma**, is normally dispensed in single doses of about 50 micrograms. Thus, each 50 microgram medicament dose of such a drug. . .

DETD More particularly, FIG. 7 is a photomicrograph of tumble-agglomerated spheronized medicament particles SM of the medicament, **beclomethasone dipropionate**. FIG. 8 is a photomicrograph of tumble agglomerated. spheronized medicament particles SM of the medicament, salmeterol, and also in the. . .

DETD Spheronised, microfine, spray-dried medicament powder of each of the two medicaments, **salbutamol** sulfate and amiloride HCl (abbreviated herein as Alb S and Amil HCl, respectively), are employed in this example. Non-spheronised spray. . .

DETD Next, a DISKHALER.TM. (a medicament dispersing device commercially available from **Glaxo** Wellcome Inc.) is employed. The 4-blister compartment is removed from the holder portion of the DISKHALER.TM., and each dosage of. . .

DETD . . . the 20 milliliter glass vial attached to the ROTAVAP.TM. as described in Example 1 above is repeated for the medicaments **beclomethasone dipropionate** and salmeterol hydroxynapthoate.

DETD A photomicrograph of the resultant spheres of **beclomethasone dipropionate** is shown in FIG. 7. From the scale noted on the photomicrograph, it can be seen that the spheres have. . .

CLM What is claimed is:

. . . particles comprise a medicament selected from the group consisting of albuterol, amiloride, terbutaline, isoproterenol, metaprotaranol,

pirbuterol, salmeterol, fluticasone propionate, budesonide, **beclomethasone dipropionate**, disodium cromoglycate, bambuterol, mometasone, insulin and triacetonide, and pharmaceutically acceptable salts thereof.

. . . the first screen are selected from the group consisting of albuterol, amiloride, terbutaline, isoproterenol, metaprotaranol, pirbuterol, salmeterol, fluticasone propionate, budesonide, **beclomethasone dipropionate**, disodium cromoglycate, bambuterol, mometasone, insulin, and triacetonide, and pharmaceutically acceptable salts thereof.

L9 ANSWER 27 OF 28 USPATFULL on STN

SUMM This invention relates to improvements in the treatment of **asthma** and other respiratory disorders. More particularly, it relates to the use of a bronchodilator drug in combination with a steroidal anti-inflammatory drug for the treatment of respiratory disorders such as **asthma**, and to pharmaceutical compositions containing the two active ingredients.

SUMM **Asthma** is a condition characterised by variable, reversible obstruction of the airways which is caused by a complex inflammatory process within. . . lungs. In most cases, this process is initiated and maintained by the inhalation of antigens by sensitive atopic individuals (extrinsic **asthma**). However, in some patients it is caused by other mechanisms which at present are poorly understood but do not involve an allergic process (intrinsic **asthma**). The disease has therefore two components, spasm of the bronchial (or breathing) tubes and inflammation or swelling of the breathing. . .

SUMM **Salbutamol**, the first highly selective .beta..sub.2 -adrenoceptor stimulant has been used successfully and effectively by inhalation for the immediate relief of spasm in **asthma**. However, when given by inhalation, **salbutamol** has usually a four to six hour duration of action, which is too short either to control nocturnal **asthma** or for convenient maintenance of the disease in some patients.

SUMM Anti-inflammatory corticosteroids such as, for example, **beclomethasone dipropionate** have also been administered by inhalation in the treatment of **asthma**, although unlike **salbutamol** the therapeutic benefits resulting from reduced inflammation may not be immediately apparent.

SUMM It has been recognized that **asthma** may be treated by using both a bronchodilator for immediate relief and a prophylactic anti-inflammatory corticosteroid to treat the underlying. . . (i.e. relief of spasm in the breathing tubes and treatment of inflammation in the breathing tubes) using a combination of **salbutamol** and **beclomethasone dipropionate** has previously been proposed (Ventide, **Glaxo** Group trade mark), but suffers a number of disadvantages in view of the above-mentioned short duration of action exhibited by **salbutamol**. Thus the need for a 4-hourly dosing regimen may discourage effective patient compliance and also renders the product less than satisfactory in the treatment of nocturnal **asthma** since the bronchodilator may not remain effective for the duration of the night, leading to impaired sleep for asthmatics troubled. . .

SUMM . . . establishment of a twice daily (bis in diem--b.i.d) dosing regimen with consequent substantial benefits in, for example, the treatment of **asthma**, particularly nocturnal **asthma**.

SUMM . . . to lead to significant improvement in daytime lung function, requirement for additional symptomatic bronchodilator and almost complete abolition of nocturnal **asthma** while giving rise to minimal systemic side effects.

SUMM . . . these two compounds to be particularly compatible and complementary in their activity and thus highly effective in the

treatment of **asthma** and other respiratory disorders.

SUMM . . . a metered dose inhaler prepared in a conventional manner or in combination with a spacer device such as the Volumatic (**Glaxo** Group trade mark) device. In the case of a metered dose inhaler, a metering valve is provided to deliver a. . .

SUMM . . . blister packs from which the powder may be administered with the aid of an inhaler such as the Rotahaler inhaler (**Glaxo** Group trade mark) or in the case of blister packs by means of the Diskhaler inhaler (**Glaxo** Group trade mark).

SUMM . . . and condition of the patient and will be determined by the clinician depending on the severity and the type of **asthma**.

DETD . . . blend is filled into hard gelatin capsules or cartridges or in specifically constructed double foil blister packs (Rotadisks blister packs, **Glaxo** Group trade mark) to be administered by an inhaler such as the Rotahaler inhaler (**Glaxo** Group trade mark) or in the case of the blister packs with the Diskhaler inhaler (**Glaxo** Group trade mark).

L9 ANSWER 28 OF 28 USPATFULL on STN

AB Pharmaceutical compositions comprising effective amounts of salmeterol (and/or a physiologically acceptable salt thereof) and **beclomethasone dipropionate** as a combined preparation for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorders.

SUMM ~~This invention relates to improvements in the treatment of~~ **asthma** and other respiratory disorders. More particularly, it relates to the use of a bronchodilator drug in combination with a steroidal anti-inflammatory drug for the treatment of respiratory disorders such as **asthma**, and to pharmaceutical compositions containing the two active ingredients.

SUMM **Asthma** is a condition characterised by variable, reversible obstruction of the airways which is caused by a complex inflammatory process within. . . lungs. In most cases, this process is initiated and maintained by the inhalation of antigens by sensitive atopic individuals (extrinsic **asthma**). However, in some patients it is caused by other mechanisms which at present are poorly understood but do not involve an allergic process (intrinsic **asthma**). The disease has therefore two components, spasm of the bronchial (or breathing) tubes and inflammation or swelling of the breathing. . .

SUMM **Salbutamol**, the first highly selective B.sub.2 -adrenoceptor stimulant has been used successfully and effectively by inhalation for the immediate relief of spasm in **asthma**. However, when given by inhalation, **salbutamol** has usually a four to six hour duration of action, which is too short either to control nocturnal **asthma** or for convenient maintenance of the disease in some patients.

SUMM Anti-inflammatory corticosteroids such as, for example, **beclomethasone dipropionate** have also been administered by inhalation in the treatment of **asthma**, although unlike **salbutamol** the therapeutic benefits may not be immediately apparent. Indeed, although the benefits of inhaled **beclomethasone dipropionate** and its safety and efficacy in **asthma** therapy are well-established in clinical practice, the true nature of **asthma** as an inflammatory disease and the consequent fundamental effects of inhaled **beclomethasone dipropionate** in its treatment have only recently been realised.

SUMM It has, however, been recognised that **asthma** may be treated by using both a bronchodilator for immediate relief and a prophylactic anti-inflammatory corticosteroid to treat the underlying. . . (i.e. relief of spasm in the breathing tubes and treatment of inflammation in the breathing tubes) using a combination of **salbutamol** and **beclomethasone dipropionate** has previously been proposed (Ventide, **Glaxo** Group trade mark), but suffers a number of disadvantages in view of the above-mentioned short duration of

action exhibited by **salbutamol**. Thus the need for a 4-hourly dosing regimen may discourage effective patient compliance and also renders the product less than satisfactory in the treatment of nocturnal **asthma** since the bronchodilator may not remain effective for the duration of the night, leading to impaired sleep for asthmatics troubled. . .

SUMM . . . of a twice daily (bis in diem - b.i.d) dosing regimen with consequent benefits in, for example, the treatment of **asthma**, particularly nocturnal **asthma**.

SUMM . . . we have found that if the .beta..sub.2 -adrenoreceptor stimulant bronchodilator salmeterol and/or a physioilogically acceptable salt thereof is combined with **beclomethasone dipropionate** in a form suitable for administration by inhalation, the resulting compositions may be administered on a b.i.d. basis to provide. . . shown to lead to improvement in daytime lung function, requirement for additional symptomatic bronchodilator and almost complete abolition of nocturnal **asthma** while giving rise to minimal systemic side effects.

SUMM . . . of the invention there are provided pharmaceutical compositions comprising effective amounts of salmeterol (and/or a physiologically acceptable salt thereof) and **beclomethasone dipropionate** as a combined preparation for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorders.

SUMM ~~The invention additionally relates to the use of salmeterol (and/or a~~ physiologically acceptable salt thereof) and **beclomethasone dipropionate** in the manufacture of pharmaceutical compositions as combined preparations for simultaneous, sequential or separate administration of salmeterol and **beclomethasone dipropionate** by inhalation in the treatment of respiratory disorders.

SUMM . . . the simultaneous, sequential or separate administration by inhalation of effective amounts of salmeterol (and/or a physiologically acceptable salt thereof) and **beclomethasone dipropionate**.

SUMM . . . a metered dose inhaler prepared in a conventional manner or in combination with a spacer device such as the Volumatic (**Glaxo** Group trade mark) device. In the case of a metered dose inhaler, a metering valve is provided to deliver a. . .

SUMM . . . blister packs from which the powder may be administered with the aid of an inhaler such as the Rotahaler inhaler (**Glaxo** Group trade mark) or in the case of blister packs by means of the Diskhaler inhaler (**Glaxo** Group trade mark).

SUMM The ratio of salmeterol to **beclomethasone dipropionate** in the compositions according to the invention is preferably within the range 2:1 to 1:40. The two drugs may be. . . inhaler will generally contain from 25 .mu.g to 100 .mu.g of salmeterol and from 50 .mu.g to 1000 .mu.g of **beclomethasone dipropionate**. As hereinbefore indicated, it is intended that the pharmaceutical compositions will be administered twice daily.

SUMM A suitable daily dose of **beclomethasone dipropionate** for inhalation is in the range of 100 .mu.g to 2000 .mu.g depending on the severity of the disease.

SUMM . . . and condition of the patient and will be determined by the clinician depending on the severity and the type of **asthma**.

DETD

Active Ingredient	Target per Actuation	Per Inhaler % w/w
Salmeterol (as hydroxynapthoate)	25.0 .mu.g	0.0448
Beclomethasone dipropionate	50.0 .mu.g	0.0647

BP

Stabiliser	7.5	.mu.g	0.0110
Trichlorofluoromethane	23.67	mg	27.8207
Dichlorodifluoromethane	61.25	mg	72.0588

DETD

Active Ingredient	Target per Actuation	% w/w
Salmeterol (as hydroxynapthoate)	25.0 .mu.g	0.0448
Beclomethasone dipropionate BP	100.0 .mu.g	0.1294
Stabiliser	10.5 .mu.g	0.0129
Trichlorofluoromethane	23.62 mg	27.7541
Dichlorodifluoromethane	61.25 mg	72.0588

DETD

Active Ingredient	Target per Actuation	% w/w
Salmeterol (as hydroxynapthoate)	25.0 .mu.g	0.0448
Beclomethasone dipropionate BP	250.0 .mu.g	0.3235
Stabiliser	25.0 .mu.g	0.0324
Trichlorofluoromethane	23.45 mg	27.5405
Dichlorodifluoromethane	61.25 mg	72.0588

DETD

Active Ingredient	Target per Actuation	% w/w
Salmeterol (as hydroxynaphthoate)	100.0 .mu.g	0.1791
Beclomethasone dipropionate BP	125.0 .mu.g	0.3235
Stabiliser	25.0 .mu.g	0.0324
Trichlorofluoromethane	23.43 mg	27.4062
Dichlorodifluoromethane	61.25 mg	72.0588

DETD In Examples 1 to 4 micronised **beclomethasone dipropionate** (as the trichlorofluoromethane solvate) and micronised salmeterol (as the hydroxynapthoate) are added in the proportions given above either dry or. . .

DETD

Active Ingredient	.mu.g/cartridge or blister
Salmeterol (as hydroxynaphthoate)	36.3
Beclomethasone dipropionate BP (anhydrous or as monohydrate)	50.00
Lactose Ph. Eur. to	12.5 mg or

to 25.0 mg

DETD	
Active Ingredient	.mu.g/cartridge or blister
Salmeterol (as hydroxynaphthoate) **Beclomethasone dipropionate** BP (anhydrous or as monohydrate)	36.25 100.00
Lactose Ph. Eur.	to 12.5 mg or to 25.0 mg

DETD	
Active Ingredient	.mu.g/cartridge or blister
Salmeterol (as hydroxynaphthoate) **Beclomethasone dipropionate** (anhydrous or as monohydrate)	72.5 100.00
Lactose Ph. Cur.	to 12.5 mg or to 25.0 mg

DETD	
Active Ingredient	.mu.g/cartridge or blister
Salmetreol (as hydroxynaphthoate) **Beclomethasone dipropionate** BP (anhydrous or as monohydrate)	72.5 200.00
Lactose Ph. Eur.	to 12.5 mg or to 25.0 mg

DETD	
Active Ingredient	.mu.g/cartridge or blister
Salmeterol (as hydroxynaphthoate) **Beclomethasone dipropionate** BP (anyhydrous or as monohydrate)	72.5 500.0
Lactose Ph. Eur.	to 12.5 mg or to 25.0 mg

DETD	
Active Ingredient	.mu.g/cartridge or blister
Salmeterol (as hydroxynaphthoate) **Beclomethasone dipropionate** BP (anhydrous or as monohydrate)	72.5 1000.0
Lactose Ph. eur.	to 12.5 mg or to 25.0 mg

DETD	
Active Ingredient	.mu.g/cartridge or blister
Salmeterol (as hydroxynaphthoate) **Beclomethasone dipropionate**	145.0 250.0

(anydrous or as monohydrate)
Lactose Ph. Eur. to 12.5 mg or
to 25.0 mg

DETD . . . blend is filled into hard gelatin capsules or cartridges or in specifically constructed double foil blister packs (Rotadisks blister packs, **Glaxo** Group trade mark) to be administered by an inhaler such as the Rotahaler inhaler (**Glaxo** Group trade mark) or in the case of the blister packs with the Diskhaler inhaler (**Glaxo** Group trade mark).

CLM What is claimed is:

1. A pharmaceutical composition comprising effective amounts of salmeterol or a physiologically acceptable salt thereof and **beclomethasone dipropionate** as a combined preparation for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorders.

. . . 1 in dosage unit form comprising 25-100 .mu.g of salmeterol or a physiologically acceptable salt thereof and 50-1000 .mu.g of **beclomethasone dipropionate** per dosage unit.

8. The use of salmeterol or a physiologically acceptable salt thereof and **beclomethasone dipropionate** in the manufacture of pharmaceutical compositions as combined preparations for ~~simultaneous, sequential or separate administration of salmeterol and~~ **beclomethasone dipropionate** by inhalation in the treatment of respiratory disorders.

9. A method of treating respiratory disorders which comprises the simultaneous, sequential or separate administration by inhalation of effective amounts of salmeterol or a physiologically acceptable salt thereof and **beclomethasone dipropionate**.

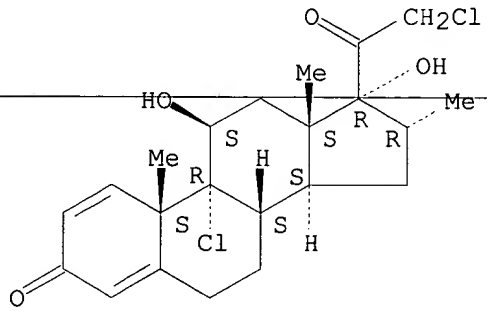
10. A method as claimed in claim 9 wherein the salmeterol or a physiologically acceptable salt thereof and the **beclomethasone dipropionate** are administered on a twice daily basis.

. . . effective amount of salmeterol or a physiologically acceptable salt thereof is 50-200 .mu.g per day and the effective amount of **beclomethasone dipropionate** is 100-2000 .mu.g per day.

=>

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 105102-22-5 REGISTRY
CN Pregna-1,4-diene-3,20-dione, 9,21-dichloro-11,17-dihydroxy-16-methyl-,
    (11.beta.,16.alpha.)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (+)-Mometasone
CN **Mometasone**
FS STEREOSEARCH
MF C22 H28 Cl2 O4
SR World Health Organization
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS,
      BIOSIS, CA, CAPLUS, CASREACT, CBNB, CIN, DRUGPAT, DRUGUPDATES, PHAR,
      PROMT, TOXCENTER, USPAT2, USPATFULL
        (*File contains numerically searchable property data)
    Other Sources: WHO

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

80 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
81 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> s mometasone furoate
4 MOMETASONE
858 FUROATE
L3 3 MOMETASONE FUROATE
(MOMETASONE(W)FUROATE)

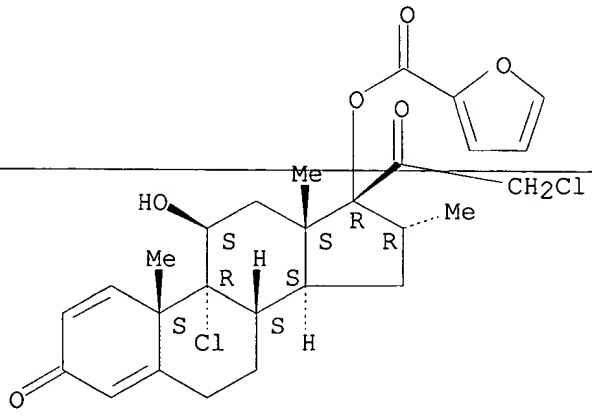
=> s mometasone furoate/cn
L4 1 MOMETASONE FUROATE/CN

=> d

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 83919-23-7 REGISTRY
CN Pregna-1,4-diene-3,20-dione,
9,21-dichloro-17-[(2-furanylcarbonyl)oxy]-11-
    hydroxy-16-methyl-, (11.beta.,16.alpha.)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Elocon
CN Mometasone 17-(2-furoate)
CN **Mometasone furoate**
CN Nasonex

CN Sch 32088
FS STEREOSEARCH
MF C27 H30 Cl2 O6
CI COM
LC STN Files: ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PROMT, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

192 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
194 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> s pirbuterol acetate
8 PIRBUTEROL
424590 ACETATE
390 ACETATES
424590 ACETATE
(ACETATE OR ACETATES)
L5 1 PIRBUTEROL ACETATE
(PIRBUTEROL(W)ACETATE)

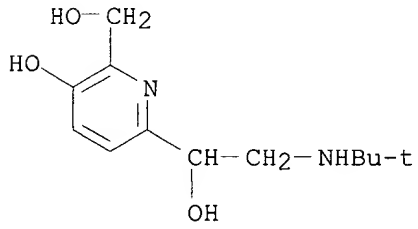
=> d

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 65652-44-0 REGISTRY
CN 2,6-Pyridinedimethanol, .alpha.6-[[(1,1-dimethylethyl)amino]methyl]-3-hydroxy-, monoacetate (salt) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Maxair
CN **Pirbuterol acetate**
MF C12 H20 N2 O3 . C2 H4 O2
LC STN Files: AGRICOLA, BIOBUSINESS, BIOSIS, CA, CAPLUS, CHEMLIST,

DIOGENES, EMBASE, IPA, PHAR, PHARMASEARCH, PROMT, TOXCENTER, USAN, USPATFULL
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

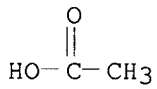
CM 1

CRN 38677-81-5
CMF C12 H20 N2 O3



CM 2

CRN 64-19-7
CMF C2 H4 O2

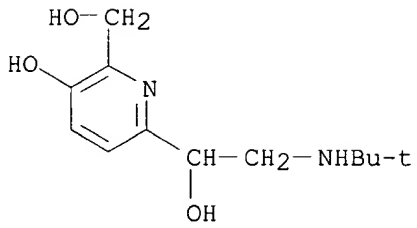


22 REFERENCES IN FILE CA (1967 TO DATE)
22 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> s pirbuterol/cn
L6 1 PIRBUTEROL/CN

=> d

L6 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 38677-81-5 REGISTRY
CN 2,6-Pyridinedimethanol, .alpha.6-[[(1,1-dimethylethyl)amino]methyl]-3-hydroxy- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (.+-.)-Pirbuterol
CN **Pirbuterol**
FS 3D CONCORD
DR 77145-72-3
MF C12 H20 N2 O3
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CEN, CIN, DDFU, DRUGPAT, DRUGU, EMBASE, IFICDB, IFIUDB, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

110 REFERENCES IN FILE CA (1967 TO DATE)
7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
113 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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